THE CHICAGO MEDICAL SCHOOL
QUARTERLY

VOLUME 16, NUMBER 3 MAY 1955

CONTENTS

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METABOLIC SYMPOSIUM:

I. HUMAN HEMOGLOBIN TYPES; A SYNTHESIS OF PRESENT KNOWLEDGE

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Signal discoveries in science seldom stand alone, even when apparently isolated facts form the core of the disclosure. Such discoveries become the keystones of further developments. A meaningful and swift illustration of this followed the announcement, five years ago, by Pauling and his associates[1] that the hemoglobin in sickle cell anemia had physical characteristics different from that of normal hemoglobin. Numerous explanations have been proffered regarding the peculiar shapes assumed by sickling cells when under changed physical conditions, but the finite clarification of the problem—that the hemoglobin itself was different and that this difference was readily demonstrable by means of electrophoresis—opened new accesses to investigation of hemolytic anemias in general and of abnormally-shaped red cells in particular.

Since the earliest formalized studies in hematology, abnormalities of red cells differentiated the anemias: pernicious anemia with its characteristic ovalomacrocytosis, poikilocytosis and anisocytosis; iron deficiency with its microcytosis and poikilocytosis; congenital spherocytosis with its characteristic red cell shape; and finally the bizarre ovalocytosis, targeting, aniso-poikilocytosis, and microcytosis of the Mediterranean syndromes.

Although mechanistic reasoning nicely explained some of the phenomena seen in pernicious anemia and iron deficiency; red cell morphology, at first so deceptively uncomplicated, later, with improved understanding became more complex and engrossing. Thus from the few simple but inaccurate and large heterogenous groups, such as von Jaksch's anemia, there have evolved finite, circumscribed, and more provocative entitites, each in itself complex, each introducing its own new problems of recognition, of definition, and of delineation. This increasingly delicate probing into a subject, made more challenging with each uncovered fragment, will continue until all possible facets have been exposed and integrated into a new totality of enlightening facts, some of which, at this time, cannot even be conjectured.

Pauling's[1] recognition in 1949 of the peculiarity of the molecular structure of sickle cell hemoglobin was soon followed by Itano and Neel's[2] recognition in 1950 of still another type of hemoglobin, since designated as hemoglobin C. Itano and Neel used the same techniques of electrophoresis employed by Pauling. Hemo-

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globin C was at first found in patients showing erythrocyte sickling, but not showing the typical genetic, clinical and hematologic pattern of sickle cell anemia. The clinical delineation of this condition was reported by Kaplan, Zuelzer and Neel[3] the next year. Simultaneously with those studies and stimulated by Pauling's investigations, Singer and his group[4] revived interest in the differences between adult and fetal hemoglobins, and introduced a simplified alkali denaturation technique, whereby these differences could be readily demonstrated. The alkali-resistant hemoglobin has since been designated F hemoglobin. By this technique, it was shown that the hemoglobin coexisting with S hemoglobin in sickle cell anemia was not normal A hemoglobin, but alkali-resistant F hemoglobin. It was further shown that significant amounts of F hemoglobin are also found in Mediterranean anemias, in some congenital spherocytoses, and occasionally in other conditions characterized by abnormal hematopoiesis.

In 1951, still another hemoglobin, D, was described by Itano[5]. Hemoglobin D has an electrophoretic mobility similar to hemoglobin S but does not cause sickling of the red cells and differs from hemoglobin S in its solubility characteristics. By 1953 hemoglobin C was found by Spaet and his associates[6] not only in combination with normal and sickle cell hemoglobins but also in the homozygous state. Its accompanying clinical and hematologic characteristics have since been more fully described by Hartz and Schwartz[7]. Interest in Mediterranean syndromes has been further stimulated by the reports of Silvestroni and his colleagues[8], who have had the remarkable opportunity to study the coexistence of sickle cell and Mediterranean anemia traits in a large group of patients.

The year 1954 brought the description of at least three, and probably four, further hemoglobins: Hemoglobin E was characterized chemically and electrophoretically by Itano and his group[9] and clinically by Chernoff, Minnich and coworkers[10, 11, 12]. This hemoglobin has a migration pattern between those of C and S hemoglobins. Edington and Lehmann[13] and H. Schwartz and Spaet[14] further described a hemoglobin, suggested as G, having a migration pattern falling between S and F hemoglobins. The hemoglobin described by Battle and Lewis[15] is probably different, inasmuch as it migrates like A hemoglobin in the commonly used veronal buffer at a pH of 8.6; however, in a cacodylate buffer at pH 6.5. and, even better, in a phosphate buffer at pH 7.8, a slower moving hemoglobin, having a mobility between S and A, becomes apparent. This hemoglobin will probably be called H, but for the moment it may be designated as X. The latest one, at this writing, is the hemoglobin described by Page, Rucknagel and Jansen[16], which so far is the slowest moving hemoglobin known, and the only one slower than A (in acid pH). It has not yet been given a designation.

To date, no characteristic abnormality has been ascribed to the hemoglobin found in congenital spherocytosis, nor has it been shown that the A hemoglobin of Mediterranean anemia is different than normal. It does not seem unreasonable to conjecture that chemical or physical differences will be uncovered in the many investigations under way. It is also likely that still other types and subtypes of hemoglobins will in time be recognized—hemoglobins causative, perhaps, for some of the more unusual hemolytic anemias encountered from time to time.

At least nine types of hemoglobins have already been described (A, F, S, C, D, E, G, H, I). If we postulate one type for Mediterranean anemia and one type for the hemoglobin of congenital spherocytosis, then there are at least eleven hemoglobins known. The postulated hemoglobin type for Mediterranean anemia may be called A_1F or M in order to indicate that there *appears* to be normal A hemoglobin accompanied by variable but significant quantities of F hemoglobin. For similar reasons the postulated hemoglobin type for congenital spherocytosis may be designated as A_2F or Sph. It is obvious that the numbers of combinations that may result in this way are unpredictable.

Clinical Syndromes Accompanying Abnormal Hemoglobins

Normal hemoglobin is the pattern seen in most people. Based on the double

allele theory, its composition is AA. This pattern, obviously, is not accompanied by either clinical or hematologic consequences.

Mediterranean Anemia, Mild (*Thalassemia Minor*)—The composition of the hemoglobin in Mediterranean anemia is A plus M. Its clinical manifestations vary. Although primarily a disease of people of the Mediterranean basin, it has been described in other Europeans, in Negroes and in Orientals. The mildest forms show no clinical stigmata of the disease, whereas in the severer forms, health and longevity are seriously impaired. Crises do not accompany the mild forms but are occasionally encountered in the severe. The degree of splenomegaly is roughly in proportion to the severity of the process. In the mildest form the spleen cannot be felt on palpation; in the severe forms the spleen may fill more than one-fourth of the abdominal cavity. Changes observed roentgenographically also vary, and range from normalcy to osteoporosity, with increased medullary width at the expense of the cortex.

Red cell values range from erythrocytosis (6 million) to moderately severe anemia; however, inasmuch as the red cells are small and thin, the color index and mean corpuscular volume are always low. There is, therefore, a disproportionately low hemoglobin level. The red cells show decided hypochromia, poikilocytosis, targeting, and often stippling. Reticulocytosis is usually moderate; however, with increasing anemia, rather high levels may be reached, and with this, nucleated red cells, in increasing numbers, make their appearance.

Evidences of hemolysis are numerous, but, again, depend in amount on the degree of the anemia. Jaundice is never prominent, although slight elevations in bilirubinemia are constant. Bile pigments are increased in the urine and stool giving rise to elevations in the hemolytic index. Red cell survival time is shortened, usually from 60 to 90 days. Erythroid hyperplasia of the marrow is constant, although seldom extreme.

Electrophoretic mobility of the hemoglobin is normal, A; but alkali-resistant hemoglobin, F, is variably increased, a characteristic feature of the disease. Although red cell production is only slightly impaired, the main defect is in hemoglobin synthesis. This is the explanation given for hypochromia of the red blood cells.

Mediterranean Anemia, Severe (*Cooley's Anemia*: *Thalassemia Major*)—The hemoglobin in severe Mediterranean anemia is composed of M plus M. The disease occurs consequent to the homozygous arrangement of the Mediterranean anemia trait and has severe clinical manifestations. In its racial characteristics, it is similar to the mild form of Mediterranean anemia. The body build is typified by stunting, a great protuberance of the abdomen secondary to the huge hepatosplenomegaly, and mongoloid facies. Patients having the severe form of the disease have a maximal life expectancy of less than 15 years. Chronic invalidism and frequently recurring hemolytic crises feature the short life. The spleen is usually huge, often filling more than half the abdominal cavity. Roentgenograms show medullary thickness and a thinning of the cortex of both flat and long bones. The skull is particularly interesting. It has been described as having a "hair-on-end" roentgenologic appearance.

Hematologic features: Profound anemia is present. The red cell level is between 1.5 and 3 million. The red cells are characterized by extreme microcytosis, anisocytosis, poikilocytosis, ovalocytosis, and targeting. Nucleated red cells are numerous and basophilic stippling is common. The color index and volume index are excessively low for the reasons given under *mild Mediterranean anemia.* Reticulocytosis may be high, especially following episodes of crisis.

Evidences of Hemolysis: There is often slight jaundice even between episodes of crisis. Urobilinogen is increased in both urine and stool and the hemolytic index is high. Red cell survival time is greatly shortened, and as a consequence there is extreme hyperplasia of the erythroid elements in the marrow. The electrophoretic pattern is characterized by normal mobility of the hemoglobin. The alkali-

resistant hemoglobin F is present in increased amounts, varying from 40 per cent to 100 per cent.

Congenital Spherocytosis—In congenital spherocytosis the hemoglobin composition is A plus Sph. Its clinical manifestations are widely variable, according to the severity of the disease which may not be as extreme as in mild Mediterranean anemia, but is otherwise similar. The disease occurs in all races. In the mild forms, it interferes with neither health nor longevity; but in severe cases, both may be impaired. Crises are common and usually follow infections. Splenomegaly is characteristically present and, although no direct correlation exists between its magnitude and the severity of the disease, the largest spleens are usually found in the severe types. Roentgenologic changes, described under *severe Mediterranean anemia,* are rare and are encountered only in the severest forms.

Hematologically there is a variable degree of anemia which, however, may be entirely absent in the compensated cases. During crises, precipitous drops in red cell count and hemoglobin may occur. The red cells are spherocytic and the color index and mean corpuscular volume are normal. Reticulocytes are invariably increased, the levels being inversely proportional to the degree of anemia. Nucleated red cells are found only after crises and in severe cases.

Evidences of hemolysis are abundant; jaundice is never present except when the disease is complicated. Slight hyperbilirubinemia, however, is constant. Because of the shortened red cell survival time, which may vary from 10 to 40 days, the hemolytic index is increased, as is the bile pigment in urine and feces. The marrow shows an erythroid hyperplasia, the severity of which depends on the degree of anemia and the recency of crisis.

The electrophoretic pattern reveals normal hemoglobin motility. The fetal hemoglobin may be somewhat elevated or within normal limits. High values have not been recorded.

Sickle Cell Trait—The hemoglobin composition is A plus S in the sickle cell trait. This is a disease primarily of the Negro, but has been reported in other races with no demonstrable racial admixture. The only clinical manifestations reported have been vitreous hemorrhage and retinopathy[17] and the occurrence of painless hematuria[18]. Patients have no physical stigmata or predisposition to other diseases. Splenomegaly is never found and there are no roentgenologic signs.

There are only two hematologic abnormalities: one is sickling of the red cells in wet preparations; the other is targeting the blood film; otherwise, all factors and indices are normal.

There is no evidence of increased hemolysis. The red cell survival time is normal and there are no marrow changes due to the condition. The electrophoretic pattern is characterized by a double peak: one revealing normal electrophoretic mobility (hemoglobin A), and the other, a more rapidly moving hemoglobin (hemoglobin S). Alkali denaturation does not reveal significantly increased amounts of F hemoglobin.

Sickle Cell Anemia—Hemoglobin composition is S plus S in sickle cell anemia, which shows the same racial predisposition revealed by sickle cell trait. Sickle cell anemia does, however, interfere with longevity and normal health. Patients having sickle cell anemia rarely live beyond 35 years and the intervening years are spent in suboptimal health, punctuated by recurrent hematologic, abdominal, or joint crisis. The body build is thin, the appearance of the patient is youthful and occasionally eunuchoid. The spleen may be enlarged in childhood but is seldom palpable beyond the twelfth year when owing to repeated splenic infarcts secondary to the aggregation of sickle cells in the splenic sinusoids, autosplenectomy occurs. During adulthood there is a further shrinkage of the spleen and at autopsy usually only small fibrotic residues are found. Roentgenologic signs of the disease are similar to those described under *Mediterranean anemia.*

There is a varying degree of anemia; the red cell count is usually under 3.5 million, and during crises may be be-

low 1.5 million. The anemia is normochromic-normocytic inasmuch as both the color index and the mean corpuscular volume are normal. Sickling and targeting are usually prominent in the dry preparation. Reticulocytes are present in large numbers and nucleated red cells are almost always found. During the recovery stage after crises, the reticulocytes rise to extremely high numbers and nucleated red cells may be numerous.

Evidences of hemolysis are found in the constant bilirubinemia with slight jaundice. Stool and urine urobilinogens are present in increased amounts giving rise to a notable elevation of the hemolytic index. The red cell survival time is greatly shortened, reports ranging between 10 and 60 days. The marrow reveals erythroid hyperplasia. Electrophoretic studies show a double peak: one for the normally migrating hemoglobin and one for the more rapidly migrating sickle cell hemoglobin. With alkali denaturation, however, the normally migrating hemoglobin is found to be highly alkali-resistant, F, rather than normal hemoglobin, A.

Hemoglobin C Trait—The hemoglobin composition is A plus C. The hemoglobin C trait has so far been reported only in the Negro. There are no clinical manifestations; there are no roentgenologic changes or episodes of hemolytic crises. The hematologic appearance is indistinguishable from normal except for the presence of target cells in the blood film.

The electrophoretic pattern reveals two types of hemoglobin; one with a normally migrating A pattern and one with a rapidly migrating C pattern. Alkali-resistant hemoglobin is present in normal amounts.

Hemoglobin C Disease — Hemoglobin composition is C plus C. The disease has so far been reported only in the Negro. Apparently it interferes somewhat with normal health and life expectancy[7]. Crises have not been described; the body build seems normal. The spleen is enlarged and shows a progressive enlargement with advancing age[7]. Roentgenologic changes are insignificant.

Hematologically, slight hypochromic anemia, lowered color index and lowered mean corpuscular volume are typical. Reticulocytes are not significantly increased. Targeting is worse in this condition than in any of the other types of hemolytic anemias. Nucleated red cells may be found occasionally but are not characteristic.

Evidence of increased hemolysis is present but not to a pronounced degree. The bilirubinemia is slight; the increase in urobilinogen and bilirubin is not notable. The hemolytic index is only slightly increased on the basis of a survival time which is approximately from 50 to 60 days. This gives rise to a moderate erythroid hyperplasia in the marrow. A rapidly migrating single hemoglobin type characterizes the electrophoretic pattern. The alkali denaturation studies reveal no appreciable increase in F hemoglobin.

Sickle C Disease—The hemoglobin composition in sickle C disease is S plus C[19]. The disease has been reported so far only in the Negro. Apparently there are normal life expectancy, health and body build. Minor crises are reported to have occurred but these do not seem to be as severe as those in sickle cell anemia. The spleen is moderately to greatly enlarged. Here too, as in sickle cell trait and sickle cell anemia, episodes of painless hematuria may occur[18]. Roentgenologic changes may be present but are not striking.

Hematologically, in sickle C disease, these is anemia, with the red cells revealing normal color index and mean corpuscular volume. The anemia usually shows a red cell range between 3.5 and 4.5 million. Reticulocytosis is the rule but it is seldom over 8 per cent. Sickling of the erythrocytes is found in both the dry and wet preparations. Targeting is prominent and occasional nucleated red cells may be seen.

Evidence of hemolysis is found in the slight elevation of serum bilirubin, in the moderate increases of bile pigment in the urine and stool, and in the somewhat elevated hemolytic index. Red blood cell survival is consider-

ably shortened and is reported to be between 20 and 40 days. Because of the shortened red cell survival, erythroid hyperplasia of the marrow is pronounced.

The electrophoretic pattern is characterized by two peaks: one at the rapidly migrating C level; and one at the intermediary S level. Alkali denaturation studies reveal no increase in F hemoglobin.

Microdrepanocytic Disease — Hemoglobin composition is M plus S in microdrepanocytic disease which characteristically occurs in Mediterranean people without proven Negro admixture. The clinical consequence of the hemoglobin abnormality is in interference with health and longevity. The degree of impairment is variable and depends on the severity of the disease. Crises have been described as primarily hematologic. The spleen is always considerably enlarged. Roentgenograms of the bones show changes varying with the severity of the disease[8].

Microcytes, anisocytosis, poikilocytosis, and sickling characterize anemia in this disease. Reticulocytosis is present, usually to a high degree. Targeting is extensive. The presence of nucleated red cells in the peripheral blood is the rule. Both the color index and the mean corpuscular volume are greatly lowered.

Evidences of hemolysis are emphatic: slight jaundice, significant increases in urine and stool bilirubin, and high elevation of the hemolytic index. Erythroid hyperplasia of the marrow is a consequence of diminished red cell survival.

Electrophoretic studies of the hemoglobin reveal double migration: one of the fast sickle hemoglobin and one at the normal level. The normal hemoglobin, however, is found on alkali denaturation study to be made up for the most part of F hemoglobin, which in this condition is always present in large amounts.

Hemoglobin D Trait—The hemoglobin composition is A plus D in the hemoglobin D trait. Our knowledge of this entity is at best fragmentary, being based on a single report in the literature[5]. Apparently the condition is not one that interferes with either normal health or longevity, nor does it seem characterized by crises. So far, it has been found only in the white race. Splenomegaly appears to be moderate. There is no anemia. Nothing can be said, to date, about evidences of increased hemolytic activity; but based on the knowledge of sickle cell D disease, it may be anticipated that an elevated hemolytic index, a shortened red cell survival time, and erythroid hyperplasia of the marrow will be found.

The electrophoretic mobility of the hemoglobin is characterized by the presence of a rapidly migrating S hemoglobin and a normal A hemoglobin. Studies have shown alkali denaturation to be normal.

Sickle Cell D Disease—The totality of our knowledge is based on two cases occurring in Caucasians[5] in whom the condition produced chronic invalidism and probable interference with normal longevity. Crises took place; the body build was poor; splenomegaly was extreme. It may be anticipated that bone changes will be seen to be extensive on roentgenologic study of additional cases.

Anemia in the cases studied was severe, varying from 1.5 to 2.5 million red cells, which showed pronounced poikilocytosis, anisocytosis and polychromatophilia, signifying decided reticulocytosis. The cells showed sickling both in the dry and wet preparations. Nucleated red cells were numerous; the color index and mean corpuscular volume were low. Again, it may be anticipated that conspicuous evidences of increased hemolysis will eventually be described, together with a greatly shortened red blood cell survival time and increased erythroid hyperplasia of the marrow.

Electrophoretic pattern was characterized by the presence of between 84 per cent and 95 per cent type S hemoglobin with the remainder of the hemoglobin being of type A. Nothing is known, to date, of the amount of alkali-resistant hemoglobin present. The solubility of the D hemoglobin, however, differs from both normal and sickle cell hemoglobin, in having a solubility characteristic that places it between sickle cell trait and sickle cell anemia. *It is this solubility difference that distinguishes D hemoglo-*

bin from sickle cell hemoglobin, for in all other particulars, the two behave in the same manner.

Hemoglobin E Trait—The hemoglobin composition is A plus E. It has been studied most extensively in Thailanders. The trait is asymptomatic. The blood shows minimal hypochromia, slight decrease in osmotic fragility, and a few target cells.

The electrophoretic pattern reveals two types of hemoglobin: one with a normally migrating A pattern and one with a pattern having a mobility intermediate between C and S. The alkali-resistant hemoglobin is normal in amount.

Hemoglobin E Disease — Hemoglobin composition E (plus a small amount of F), is a disease so far only reported in Thailanders. It gives rise prominently to symptoms of fatiguability, arthralgias and jaundice, and to physical signs of splenomegaly or hepatomegaly.

Among the blood changes is a striking microcytosis without anemia or reticulocytosis. From 25 to 60 per cent of the red cells show targeting. There is slight erythroid hyperplasia of the marrow as well as a right shift in the osmotic fragility.

The electrophoretic pattern reveals a simple pattern of migration, intermediate between C and S, except for the slight amount of F hemoglobin which accounts for 2 to 6 per cent of the total.

Hemoglobin F—Mediterranean Disease —Hemoglobin composition E plus F. The disease has so far been reported only in Thailanders. The clinical disease is reminiscent of Cooley's anemia, although its course is milder and most of the afflicted live to adulthood, require fewer transfusions, lack the "mongoloid facies," and show less cachexia than in Cooley's anemia. Splenectomy is thought to have an alleviating influence on the course of the disease. Hematologic evidences all point to a severe hemolytic process, there being elevations in the reticulocytes, the erythrocyte hypertrophy in the marrow and the hemolytic index. The red cells show the changes of Cooley's anemia, except for the hypochromia, which is less marked. From 5 to 20 per cent of the red cells are targeted and their resistance to osmotic fragility is increased.

The electrophoretic pattern reveals from 60 to 80 per cent of the hemoglobin to migrate at a rate between C and S and from 20 to 40 per cent as F hemoglobin, which agrees with values found by the alkaline denaturation technique.

Hemoglobin G Disease — Hemoglobin composition is G. There are no important clinical consequences. The blood picture resembles that of mild Mediterranean anemia.

The electrophoretic mobility of the hemoglobin lies between S and F.

Hemoglobin G—Sickle Cell Disease— Hemoglobin composition is G plus S. The clinical consequences are splenomegaly and bone changes; the hematologic consequences, a moderately severe hemolytic anemia resembling that seen in microdrepanocytic disease, with increased osmotic resistance of the red cells and demonstrable sickling.

The electrophoretic pattern reveals part of the hemoglobin migrating as S hemoglobin and past faster than S, but slower than F.

Hemoglobin H (or X) Trait—Hemoglobin composition is indistinguishable from normal at pH 8.6 by paper electrophoresis, or in phosphate buffer at pH 9.2 with Tiselius technique. Resolution into two components may be had by either cacodylate buffer at pH 6.5 or phosphate buffer at pH 7.8 by Tiselius technique. Under conditions of the second experiment, 75 per cent of the hemoglobin is found to migrate to a point between A and S, while the remainder migrates normally.

The condition so far has been reported only in two white adult siblings (male and female), who had pallor, mild jaundice, and splenomegaly. The red cells showed conspicuous poikilocytosis, hypochromia, and targeting. Sickling could not be produced. The alkali-resistant hemoglobin was slightly increased.

Hemoglobin I (or Y) Trait—Hemoglobin composition is I plus A. No clinical or hematologic consequences of the trait were reported in six members, both sexes, of a Negro family through three generations. The homozygous state (Hemoglobin I Disease) has not yet been described.

The electrophoretic pattern (veronal buffer pH 8.6) reveals 80 per cent of the hemoglobin migrating normally, and 20 per cent migrating at a rate faster than A.

Anticipated Types—The discovery of undescribed hemoglobin types will be governed entirely by chance, aided by searching awareness of their possible presence, because their occurrence will be limited by the coupling of rare or relatively uncommon factors. Most of the anticipated hemoglobin diseases may be expected to have profound clinical and hematologic consequences, factors which in themselves make these conditions self-limiting. Occurrence of these disorders is likelier in the young, inasmuch as prolongation of the line and perpetuation of the disease are unlikely by reason of shortened life span.

Discussion

So far all abnormal hemoglobin types have been found to result in an alteration of the shape of the red blood cells. This seems to be the one common denominator. The second most prevalent feature, to which sickle cell trait (Hemoglobin SA) is the only exception, is the shortened survival of the red cell. It is likely that the alteration in the red cell shape contributes significantly to the

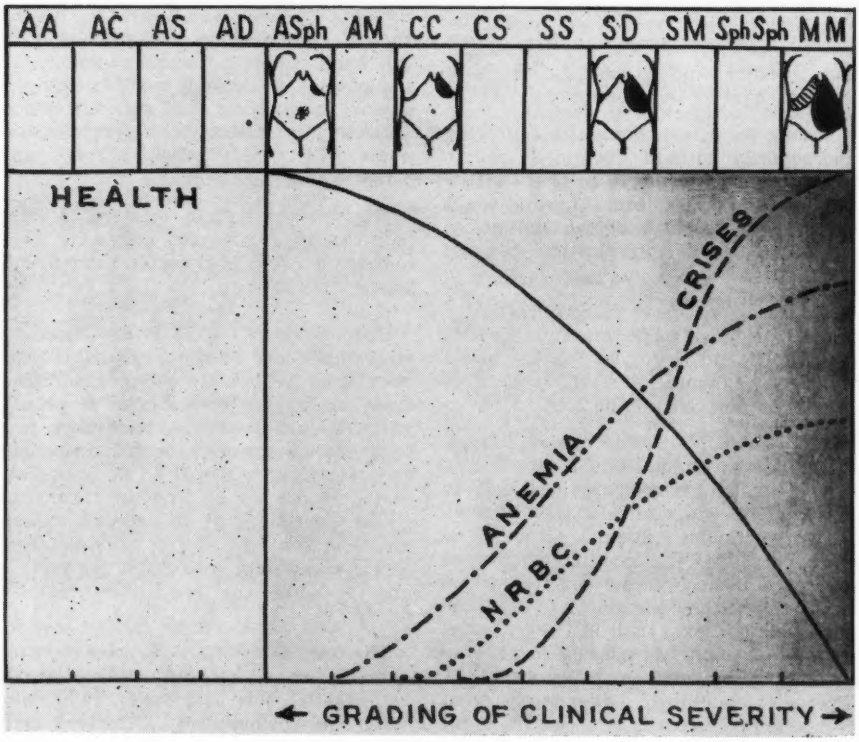

CHART 1

Correlation of human hemoglobin types with clinical and hematologic manifestations. The chart indicates the consequences of the more common hemoglobin combinations.

shortened life of the cell, but it is unlikely that this is the only determinant.

Although by electrophoretic and chemical means, most of the hemoglobins so far described can now be differentiated, there still remain some (congenital spherocytosis, paroxymal noctural hemoglobinuria, and other atypical hemolytic anemias attributable to intracorpuscular factors), whose recognition depends on indirect and circumstantial evidence.

Since by definition, shortened red cell survival is the essential characteristic of hemolytic anemias, other evidences of hemolysis will be found. These evidences fall into two categories: those evidences secondary to red cell disintegration and those secondary to a compensatory regeneration. In the first category are evidences of increased pigment metabolism; such as bilirubinemia, hyperurobilinogenuria and increased urobilin in the stool; as well as increase in the size of the spleen, a finding to which only sickle cell anemia and hemoglobin C trait are exceptions. Because blood breakdown may be episodic and at times more vigorous than at other times, the clinical as well as the hematological course may be punctuated by acute exacerbations (crises). Among other consequences of the anemia, may be mentioned the coexisting suboptimal health and development with actual incompatibility with normal life expectancy in some of the graver forms of the disease. The latter is especially true in the presence of homozygous abnormal hemoglobins, as in sickle cell anemia and severe Mediterranean anemia. Of incidental secondary importance in this connection is the frequency of gallstones (bilirubin) and leg ulcers.

As interesting as are the evidences of erythrocyte disintegration, the evidences of compensatory regeneration are even more interesting. Simplest and most direct is the increase in young red cells, the reticulocytes. Secondary evidence is found in the marrow where extensive hyperplasia, particularly with a proliferation of erythropoietic elements, is the rule. In the more serious forms of the hemolytic anemias, as well as during the periods following crisis, nucleated red cells, sometimes in great numbers, may be found. This marrow hyperplasia explains the increase in porosity of the medullary cavity and the thinning of the cortex which characterizes the changes seen roentgenographically in hemolytic anemias.

Although of neither practical nor diagnostic importance, the archaic saline fragility test has sufficient historical and literary significance to deserve mention. In all the hemolytic anemias under discussion, with the exception of congenital spherocytic anemia, the resistance to hypotonic salt solution is increased. The explanation for this is entirely physical and depends on the increased ratio of surface area to cell volume, a factor also responsible for the phenomenon of targeting and the apparent hypochromia of the cells.

Summary

1. In 1949 Pauling and his associates reported that the hemoglobin in sickle cell anemia had physical characteristics different from that of normal hemoglobin and that this difference was demonstrable by means of electrophoresis.

2. In rapid developmental succession, investigations into hemolytic anemias in general, and into abnormally shaped red cells in particular, have so far led to the differentiation of nine types of hemoglobin: A, F, S, C, D, E, G, H, and I. Their clinical deviations from normal have been delineated. A further type is herein postulated for Mediterranean anemia: A_1F or M, and still another for the hemoglobin of congenital spherocytosis: A_2F or Sph.

3. The clinical syndromes with the hematologic features and evidences of hemolysis accompanying the known abnormal hemoglobins, as well as the electrophoretic patterns by which they are demonstrated, are restated. These syndromes include both mild and severe Mediterranean anemia, congenital spherocytosis, sickle cell trait, sickle cell anemia, hemoglobin C trait, hemoglobin C disease, sickle C disease, microdrepanocytic disease, and the more recently

described rare clinical sydromes associated with D, E, G, H, and I hemoglobins.

4. The common denominator of all abnormal hemoglobin types is an alteration of the shape of the red cells. This may contribute to the second important feature: the shortened red cell survival which is the essential characteristic of hemolytic anemias. (Sickle cell trait, hemoglobin SA, is the only exception.)

5. Other evidences of hemolysis are found (1) secondary to red cell disintegration and (2) secondary to a compensatory regeneration. These observed and presumptive evidences are depicted.

6. It is suggested that if A is designated as the normal, then the commoner hemoglobin types may be graded in the order of increasing clinical consequences as A, C, S, D, Sph, M. Their severity and clinical effects, when present either alone or in combination, are outlined in the conclusions.

7. The atypical hemolytic anemias whose recognition depends on indirect and circumstantial evidences are discussed.

Conclusions

1. Just enough has been learned of the hemoglobin types to allow a "grading" according to the severity of their clinical consequences. If we use A as the normal, the commoner hemoglobins may be graded in the order of increasing consequence as follows: A, C, S, D, Sph, and M.

2. Hemoglobin C combined with A is productive of a mild hemolytic anemia, without consequence. Even in the homozygous state, CC, the disease is not severe, even though accompanied by frank hemolytic anemia and splenomegaly.

3. S in combination with A produces targeting, but otherwise nothing abnormal. Even when S is combined with C, the consequent disease is relatively mild. It is only when S is homozygous or combined with F, with D, or with M hemoglobin that clinical and hematologic manifestations become serious.

4. Hemoglobin D apparently is of more consequence; its heterozygous form combined with A giving rise at least to splenomegaly, presumably secondary to increased hemolysis. Its homozygous form is so far unknown but may be expected to be rather severe. Certainly when D is combined with S, the consequent hemolytic anemia is worse than that seen with C.

5. Hemoglobin Sph is always important because of the conspicuously shortened life of the spherocyte. This generally leads to unequivocal evidences of hemolysis, and the predisposition to crises increases the seriousness.

6. Hemoglobin M seems to carry the greatest threat. Its combination with A hemoglobin leads to hemolytic anemias of varying severity. Its homozygous form is incompatible with life beyond the fifteenth year. When combined with S hemoglobin the resulting disease is only somewhat less severe than the homozygous form.

7. The presence of F hemoglobin in large amounts in combination with either A, as in Mediterranean anemia; or with S as in sickle cell disease, is probably important in the pathogenesis of these severe hemolytic syndromes. Its exact effect is deserving of further study.

8. In an era of medical thinking, when more and more emphasis is being placed on laboratory procedures, everything should be done to free the clinician, rather than make him more dependent on the laboratory. The very nature of progress and changing concepts partly negates this wish, however, as the observations recounted here bear out. The half-blind recognition, for example, that many cases existed which were dismissed as atypical "sickle cell anemia," because they did not fulfill the criteria of either the "trait" or the "disease," permeated the literature and puzzled the clinician, the hematologist, and the geneticist alike. Apparently casual observations in the chemical laboratory, far from the bedside or the clinical laboratory, have impelled new investigations into a group of varied, provoking, and little understood disorders.

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II. THE PHYSIOPATHOLOGY OF DIABETES*

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Introduction

The classic experiments of Mering and Minkowski[99] on the production of experimental diabetes by removal of the pancreas; followed 33 years later by the discovery of insulin[9] led to the belief that the primary defect in diabetes mellitus is insulin insufficiency. However, evidence in support of this hypothesis has become available only recently. Insulin insufficiency can be absolute, as result of either decreased production or excessive destruction; or it can be relative, as a result of either increased metabolic demand or oversecretion of "anti-insulin" hormones.

Absolute Insulin Insufficiency

A. *Decreased production.* In 1901, Opie[105] described hyalinization of the islets of Langerhans in diabetes, and suggested that this lesion is characteristic for the disease. Although this observation has been confirmed repeatedly, in many cases of diabetes the islets have normal appearance, at least when examined by common histologic technics[132]. With the development of more specific staining methods,[55,104] it has become apparent that human diabetes is often associated with partial or complete degranulation of the beta calls. Bell[15], for example, studied the pancreas obtained at autopsy of 995 cases of diabetes and found complete or partial degranulation in all subjects under 20 years of age, who were suffering from severe juvenile diabetes; in 79.5 per cent of the patients between the ages of 20 and 40; in 48.2 per cent of those between the ages of 40 and 60; and in 33.6 per cent of those over 60 years of age. In this large series of cases, the extent of degranulation appeared to have been proportional to the severity of diabetes up to the age of 50; although, in older patients a correlation could not be demonstrated. Other studies indicate that with the decrease in beta granules, there is a proportional decrease in insulin content of the pancreas[62] and, with it, an increase in the severity of diabetes[139]. Beta cell degranulation can also be observed in a variety of experimental conditions in which there is a reduction in the insulin content of the pancreas, accompanied sometimes by temporary diabetes. Examples of these conditions are: fasting, diets restricted to fat, daily injections of insulin[11], and the oral[76,137], intraperitoneal[32] or intravenous[12] administration of large quantities of glucose (glucose, when administered by continuous infusion, may cause extensive pancreatic necrosis without diabetes[80]). This and other evidence suggests that the beta granules represent a precursor of insulin, and that degranulation is a sign of decreased insulin production. By means of sensitive bio-assay methods for the determination of insulin in the blood[19,107], the confirmation of this hypothesis became possible with the demonstration that the insulin content of the blood is decreased in diabetes, increased in the presence of islet cell adenoma, and that insulin may disappear completely from the blood of patients in diabetic coma and/or depancreatized animals[59,88]. The reason for this decreased insulin production in diabetes is not known. It has been suggested that SH-groups are necessary for the synthesis of insulin; diabetes may be related to a decrease in the concentration of glutathione and other SH-containing substances in the blood. This hypothesis is based on the following observations: (1) glutathione protects against the diabetogenic effects of alloxan and of steroid hormones[27]; (2) SH-containing BAL improves the glucose tolerance of diabetic patients[23]; (3) glutathione depletion makes the animal susceptible to alloxan and to other purines like uric acid, which normally are not diabetogenic[58]; (4) alloxan-like materials have been found in normal animal tissues and

*Based on a lecture given at the meeting of the Department of Medicine of The Mount Sinai Hospital of Chicago on February 23, 1955.

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fluids[130]; (5) ACTH and cortisone administration cause a decrease in blood glutathione level[66]; (6) a lipoprotein obtained from the serum of diabetic rats inhibits both glutathione synthesis by rat liver slices and glucose uptake by rat diaphragm; its action is partially reversed by insulin[12].

B. *Increased insulin destruction.* Many years ago, Arborelius and Akerren[2] found that insulin is less active when injected into the portal system than when injected subcutaneously and suggested that its rapid disappearance may be due to destruction in the liver. This destruction, observed also by others[7, 37, 57, 63, 89, 102, 103, 133, 134], appears to be due to an equilibrium between the insulin-destroying enzyme, insulinase, and a specific insulinase-inhibitor[37, 63, 102, 103]. The presence of an insulin-neutralizing factor in the serum of an insulin-resistant patient was also described recently[120]. Although sufficient data on liver and kidney insulinase and insulinase-inhibitor or on serum insulin-neutralizing factor in diabetes are not available, the suggestion has been made that a relative increase in insulinase activity may be responsible, at least in part, for the phenomenon of insulin insufficiency[103], and, conversely, that a decrease in insulinase activity in the kidney may be responsible for the decrease in insulin requirement observed in some cases of Kimmelstiel-Wilson disease[35]. Insulin degradation is also inhibited by 5-isopropylidene-2, 4-dithiohydantoin or MC2346[37], a synthetic compound reported to be effective in reducing the incidence of diabetes in rats after partial pancreatectomy[70]. The possible implications of these interesting findings towards the therapy of diabetes and for an understanding of the phenomenon of insulin resistance are obvious and deserve further investigation.

Relative Insulin Insufficiency

A. *Increased metabolic demand.* The metabolic and dietary factors affecting the islets of Langerhans have been reviewed recently[16, 60]. The evidence indicates that either a high caloric or carbohydrate intake or the injection of large quantities of glucose are among the factors capable of stimulating islet activity in the animal[50] and, possibly, in man[112], by increasing the demand for insulin[39]. In most cases when the pancreatic reserve is normal, insulin production keeps pace with the increased demand; the individual becomes obese and no signs of carbohydrate intolerance develop. In other cases, when the pancreatic reserve is low, this adjustment is not possible and a situation of relative insulin insufficiency is created. Still in other cases when the stimulation of the islets becomes excessive, the insulin-secreting cells may degenerate, insulin insufficiency may become absolute and diabetes may follow. Excessive stimulation and subsequent degranulation of the islets can be prevented if the increased insulin demand is met with the administration of insulin, or is reversed by restricting caloric and carbohydrate intake. This may explain the beneficial effect of weight reduction on the glucose tolerance of middle-aged, obese diabetics.

B. *Excessive secretion of "anti-insulin" hormones.* The term "anti-insulin hormones" has appeared repeatedly in the recent literature to indicate hormones mobilized in response to insulin hypoglycemia and capable of raising the blood sugar[44]. This term does not necessarily imply that these hormones can either destroy or neutralize insulin, or that they have any action opposite to that of insulin, other than that of raising the blood sugar level. If we accept this definition, we may divide the anti-insulin hormones into quick-acting and slow-acting types. The quick-acting hormones raise the blood sugar by promoting glycogenolysis; while the slow-acting hormones raise the blood sugar by promoting gluconeogenesis, by inhibiting glucose utilization and, possibly by other means. When secreted in normal amounts, these hormones help to maintain a normal carbohydrate metabolism[45, 46]; when, *viz.* after prolonged insulin hypoglycemia[98, 124], the secretion of these hormones is increased, they may cause a temporary decrease in carbohydrate tolerance accompanied by "paradoxycal" hyperglycemia. In this manner insulin hypoglycemia begets hypergly-

cemia, or, as it has been stated, insulin becomes "diabetogenic."

1. *Quick-acting hormones.* This category includes epinephrine, glucagon and, perhaps, the hormones of the posterior pituitary. The hormones of the posterior pituitary have a hyperglycemic effect only in large doses[56]. They cause glycogenolysis in the uterine but not in the skeletal muscle[86] and it seems doubtful that this effect may be of sufficient magnitude to cause a significant elevation of blood sugar. There is no evidence that they are secreted in response to insulin hypoglycemia. On the other hand, epinephrine is secreted in response to insulin hypoglycemia as shown by a depletion of the adrenal medulla[67] and by an increase in epinephrine content of the adrenal blood[36]. Epinephrine causes hyperglycemia by promoting liver glycogenolysis[129]; in addition, it may stimulate the secretion of anterior pituitary hormones[108] which, in turn, have hyperglycemic action. Glucagon is also secreted in response to hypoglycemia[44-46, 97] and elevates the blood sugar by promoting liver glycogenolysis[129]. According to recent investigations in eviscerated animals, glucagon retards the transfer of glucose from the extracellular to the intracellular compartment and, therefore, indirectly inhibits its utilization[34]. In addition, according to some investigators, glucagon inhibits the effect of insulin on the glucose uptake by rat diaphragm[116] and on the synthesis of glycogen by muscle[109]. Thus glucagon appears to be an "anti-insulin" hormone in more ways than one. According to other investigators, however, glucagon does not inhibit the peripheral utilization of glucose[131] but by raising the blood sugar may actually stimulate it. For this reason, glucagon has been called a synergist of insulin[22, 38]. These results however, were obtained in intact men and animals, in which the pancreas may have responded to glucagon hyperglycemia with an increase in insulin secretion, and the true effects of glucagon may have been obscured.

2. *Slow acting hormones.* This category includes: anterior pituitary growth hormone (somatotrophic hormone or STH), adrenocorticotrophic hormone (ACTH), prolactin, hormones of the adrenal cortex and sex hormones.

STH—The classic experiments of Houssay and Biasotti[68], Young[140], Lukens[92] and many others[141] have demonstrated that hypophysectomy leads to "amelioration" of pancreatic diabetes. This observation was reconfirmed recently in diabetic patients subjected to hypophysectomy[85] or suffering from pituitary necrosis[4, 94, 110, 118]. On the other hand, the administration of anterior pituitary extracts (APE) causes impairment of glucose tolerance and increased resistance to insulin. This disturbance may be either temporary (idiohypophyseal diabetes) or permanent (metahypophyseal diabetes). Pituitary diabetes can also be obtained with purified STH preparations[24, 31] and appears to be the result of both direct and indirect actions on the pancreas. Direct actions, such as stimulation of the secretion of glucagon[21, 49] and inhibition of the secretion of insulin in response to glucose[5], may explain the hyperglycemic effect of intravenous injections of STH[40, 49, 84]. Prolonged STH hyperglycemia, due to repeated injections, may stimulate the pancreas indirectly by creating an increased demand for insulin. As in the case of high carbohydrate intake, the pancreas of some animals (rats, puppies) responds to this stimulation by signs of increased function such as hypertrophy of the islets[60], increase in plasma insulin[111] and in glycogen deposits[74], and hypoglycemia[101]. On the other hand in other animals (adult dogs or animals with decreased pancreatic reserve[24, 101, 142]), this excessive stimulation causes degranulation of the beta cells, decreased insulin content of the pancreas[24], and permanent diabetes. These direct and indirect effects on the pancreas, however, cannot be the sole explanation of the diabetogenic action of STH, for this can be observed also in the depancreatized animal where STH causes an increase in hyperglycemia and glycosuria[25, 71]. Recent evidence suggests that the extrapancreatic action of STH may be based on an insulin-reversible inhibition of glucose utilization by the muscle[20, 87, 126], possibly through the hexokinase reaction[18].

ACTH. The mechanism of the diabetogenic effect of ACTH is not fully understood and may be due entirely, or in part, to increased secretion of adrenal corticalhormones. The available evidence suggests that ACTH may enhance the effects of STH[113] and glucagon[65] and it may inhibit glucose uptake by the tissues[31,87]. The resulting hyperglycemia would stimulate the islets of Langerhans[3,83] and lead to degranulation and exhaustion. It has been suggested that ACTH may exert its effects by decreasing the supply of SH-groups available for the synthesis of insulin and for the activity of several enzymes necessary for carbohydrate metabolism, including hexokinase[6,8,27,28,66,75,89].

Prolactin. The diabetogenic effect of anterior pituitary extracts containing prolactin was first reported several years ago[52]. However, only recently purified prolactin preparations have become available, and it has been possible to investigate its diabetogenic properties under better experimental conditions. Prolactin decreases insulin sensitivity and glucose tolerance in hypophysectomized and in hypophysectomized-adrenalectomized dogs[30]. In normal dogs, prolactin, at first, causes hypoglycemia associated with profound degranulation of the beta cells[48] and with the liberation of insulin into the blood of the pancreatic vein[47], while, after repeated injections, prolactin causes hyperglycemia. This suggests that prolactin may cause a rapid dumping of preformed insulin, followed by decreased production[48] and diabetes[72]. Since prolactin aggravates hyperglycemia in the depancreatized animal, it also must have some extrapancreatic action, in addition to its action on the beta cells: the sequence of decreased pancreatic reserve, increased insulin demand, and stimulation and exhaustion of the beta cells may also apply to this hormone.

Adrenal Cortical Hormones. Like hypophysectomy, adrenalectomy causes a dramatic "improvement" of diabetes in animals[91] and in man [93,138]. On the other hand, the administration of adrenal cortical hormones[17,95] enhances the diabetogenic effect of STH[1] and decreases glucose utilization *in vitro*[8,20,87,126] and *in vivo*[13], especially in those non-diabetic relatives of diabetic patients who already have a low pancreatic reserve[41]. The observation that adrenal cortical hormones cause a marked hypertrophy and hyperplasia of the residual islets of Langerhans in partially depancreatized and ovariectomized rats[73] and degranulation of the beta cells[64] suggests that the diabetogenic effect of adrenal cortical hormones may also be the result of beta-cell stimulation and exhaustion.

Sex Hormones. The importance of the gonads in diabetes has been re-emphasized recently by the observation that subtotal pancreatectomy in rats is followed by a 100 per cent incidence of diabetes in males, but only 40 per cent in the females and that castration increases the incidence in the females and decreases it in the males[69]. The administration of estrogens at first causes hyperglycemia and glycosuria. However, after prolonged treatment, not only does this diabetogenic effect disappear, but the incidence and severity of diabetes in alloxanized rats decreases and as many as 47 per cent of them are cured, especially if also treated with insulin[79,115]. The antidiabetic effect of estrogens can be seen in acromegaly and also in the capon[128], where estrogens bring about a reversal of the abnormal glucose tolerance curve[46]. This action of estrogens may be due either to stimulation of islet growth[82,115] or to inhibition of STH production by the anterior pituitary[96]. Androgens, on the other hand increase the incidence of diabetes[73]. Certain derivatives of progesterone also have a diabetogenic effect[77].

The Mechanism of Insulin Action

The mechanism of insulin action has been reviewed recently[14,125]. Several possible sites of insulin action are indicated: (1) insulin may promote the transfer of glucose from the extracellular to the intracellular fluid[33,54,90,106,135]; (2) insulin may increase the oxidation of glucose[43,119,136]; (3) insulin may promote phosphorylation[26], as indicated by its effect on the rate of transport of labelled phosphate into the rat diaphragm[119], by its effect on the phosphorylation of thiamine[51,122], and on the hexokinase (gluco-

kinase) system[114]. Insulin does not influence the action of fructokinase[114] and hence the utilization of fructose[29]. Accordingly, the diabetic appears to utilize fructose normally[100], a fact which led to renewed interest in this sugar for the dietary management of diabetes[117, 121, 123]. In addition to its actions on carbohydrate metabolism, insulin exerts an effect on the metabolism of proteins and lipids. For a review of these actions and of the complex relationships between diabetes, serum lipoproteins and atherosclerosis, the reader is referred to recent comprehensive reviews[10, 14, 16, 42, 53, 61, 81, 125, 127].

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III. THE ADRENO-GENITAL SYNDROME

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Introduction

Adrenocortical hyperfunction can result in two distinct types of clinical conditions; namely, Cushing's syndrome and the adrenogenital syndrome. In the pediatric age group the latter is overwhelmingly more common than the former. The sex distribution favors the female four to one over the male. The adrenogenital syndrome is probably the commonest adrenal disorder in childhood.

Although this syndrome is rare, its manifestations deserve emphasis because the differential diagnosis is formidable. While the chemistry, mechanism of action, site of production and other properties of the adrenal steroids were being elucidated (*Figure* 1), the pathophysiology of this disease remained obscure. It was not until Dr. Lawson Wilkins' brilliant work and his introduction of cortisone therapy that the condition began to be generally understood. The investigations of Jailer, Talbot and Kelley served to strengthen Wilkins' theory.

Pathophysiology

In congenital adrenal hyperplasia (*Figure* 2**), the enzyme systems in the adrenals favor the production of androgens over the salt regulating steroids and corticosteroids. The result is that the adrenal produces predominantly androgenic steroids, which do not suppress ACTH production, resulting in further stimulation of androgens. It is clinically important that oftentimes there is a sodium losing and potassium retaining component in conjunction with this abnormal steroid production.

The clinical sequelae of this state of affairs are:

1. Pseudosexual precocity in the male (the gonads are not developed, opposed to true sexual precocity);
2. Masculinization in the female, and often female pseudohermaphroditism;
3. A salt losing Addisonian-like crisis, which is of greatest significance in the new born period;
4. Very rarely, hypertension, hypoglycemia, or skin pigmentation.

Recent work has demonstrated directly a low level of 17-hydroxycorticosteroids in the blood and urine of these patients, with high levels of blood ACTH. The low blood levels of 17-hydroxycorticosteroids are not significantly elevated after the injection of ACTH.

Clinical Picture in the Female

The congenital form is characterized by pseudohermaphroditism, with a persistent urogenital sinus which has failed to differentiate into urethra and vagina. The clitoris is hypertrophied and resembles a hypospadic penis. The labia majora are large and surround the urogenital sinus, giving a scrotal appearance. These patients are often inadvertently reared as boys. Growth proceeds at an accelerated rate, but because of the early closure of the epiphyses the eventual stature is short. Pubic and axillary hair appear early, muscular development is rapid, the voice deepens, the breasts are atrophic, and the clitoris continues to enlarge. The urinary excretion of 17-ketosteroids is unusually high, and the bone age is markedly advanced.

In the postnatal form the picture is the same, except for a lack of pseudohermaphroditism.

Clinical Picture in the Male

In the male, the syndrome is characterized by the early development of pseudosexual precocity. The phallus is markedly enlarged; however, the testes are either small or consistent with chronological age. Axillary and pubic hair develop precociously and muscular de-

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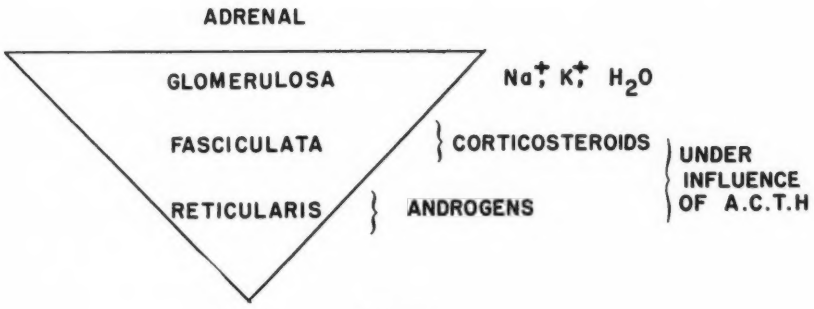

FIGURE 1

velopment is far advanced, giving the appearance of the little Hercules (*Macrogenitosomia precox*). Growth is accelerated, but again the eventual stature is short. The bone age is advanced. Urinary 17-ketosteroids are elevated.

Clinical Picture in the Newborn with a Salt Losing Component

In the newborn period, the infant with the adrenogenital syndrome with a salt losing component is a pediatric emergency. In the female the diagnosis is usually not too difficult because of the associated pseudohermaphroditism. Therefore, if the pseudohermaphroditism is recognized at birth, and the patient is not considered as a male after superficial observation of the enlarged phallus, we may then be on guard for the development of an Addisonian-like crisis. On the other hand, in the male, *macrogenitosomia precox* is usually not manifest at birth. The most consistent feature of the Addisonian-like crisis in the neonate is vomiting, often of a projectile nature. Many of these infants have had exploratory surgery, even pylorotomy. Dehydration, lethargy, increased nasopharyngeal mucus, cyanosis, abnormal neurologic signs (poor Moro reflex, hypotonia, weak suckling), circulatory and respiratory imbalance, and shock complete the clinical picture.

If the diagnosis of congenital adrenal hyperplasia is considered, it may easily be confirmed or denied. The serum sodium reaches unusually low levels, even in the face of severe dehydration, whereas the serum potassium is markedly elevated. Further confirmatory laboratory evidence is to be found in the elevation in the twenty-four hour excretion of 17-ketosteroids.

Inheritance

The disease is known to occur in families. Until recently, with the advent of cortisone therapy, these patients have not reproduced. Simple Mendelian dominance or recessiveness cannot explain the mode of inheritance. The parents are apparently normal people. In some families there is only a sporadic case, whereas in others, all of the children are affected. An example is the normal woman, who produced a normal child with her first husband; however, all three children fathered by her perfectly normal second husband developed the adrenogenital syndrome.

Differential Diagnosis

Differential diagnosis of the adrenogenital syndrome may be protean in nature.

In the newborn period, gastritis of the newborn, tracheo-esophageal fistula, diaphragmatic hernia, cardio-chalasia, pyloric stenosis, pylorospasm, cerebral birth trauma, congenital central nervous system anomalies, meningitis, sepsis, gastroenteritis, duodenal atresia, annular pancreas, subdural hematoma, gastro-intestinal allergy, anomalies of gastro-intestinal fixation and rotation, as well as adrenal hemorrhage or tumor may enter into the differential diagnosis.

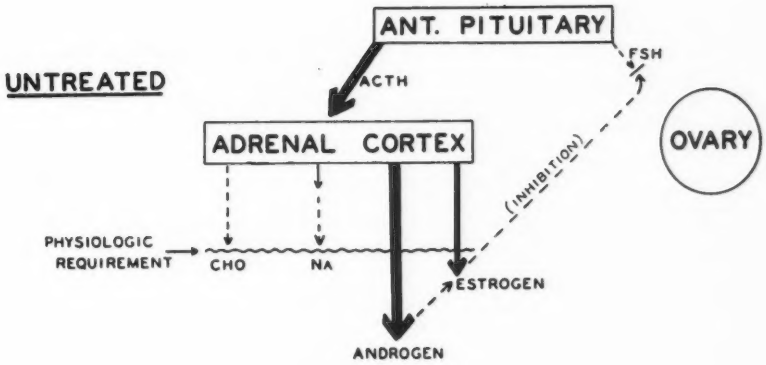

FIGURE 2*

The female pseudohermaphrodite must be differentiated from the true genetic intersex, from the male with severe hypospadius and bilateral cryptorchidism, and from adrenal tumor.

Macrogenitosomia precox must be differentiated from true precocious puberty (constitutional, hypothalamic-pituitary, testicular, and from adrenal tumor).

Whenever there is an associated salt losing component, implication of the adrenal gland is usually accomplished with relative ease. In the female pseudohermaphrodite, who has no significant abnormality of salt regulation, the marked elevation of urinary 17-ketosteroids points directly to the adrenals. In the patient with *macrogenitosomia precox*, who has no significant abnormality of salt regulation, the hypothalamic-pituitary axis may be ruled out by the relatively small and immature testes (confirmed by testicular biopsy if any doubt remains). Precocious puberty of testicular origin may be ruled out by the absence of a testicular tumor (confirmed by testicular biopsy if any doubt remains).

Therefore, by the use of clinical evaluation and relatively simple laboratory procedures, the adrenal gland may be diagnosed as the origin of the disturbance in any of the possible clinical pictures.

However we must still differentiate the newborn with adrenal hemorrhage or adrenal tumor and the older child with adrenal tumor.

The problem of differentiating adrenal hemorrhage in the newborn is not very significant, because both the adrenogenital syndrome with a salt losing component and adrenal hemorrhage require similar therapy, *i.e.*, adrenal and salt replacement. However, there are certain easily demonstrated differences. Associated female pseudohermaphroditism speaks for congenital adrenal hyperplasia. Elevated urinary 17-ketosteroids are expected in the adrenogenital syndrome, whereas diminished to absent urinary 17-ketosteroids are expected in adrenal hemorrhage.

The problem of differentiating adrenal tumor, at any age, is a very significant one. The adrenogenital syndrome is suggested by a family history, when present, and history of onset at birth, when present; however, these are not conclusive differentiating points. The adrenogenital syndrome occurs more often in the pediatric age group than does adrenal tumor, but this also does not make for conclusive differentiation. The clinical picture and routine laboratory determinations may be exactly the same in both conditions.

Roentgenography with retroperitoneal

**Figs. 2 and 3 were taken from Wilkins, L.: Tools and Methods of Diagnosis and New Trends in the Treatment of Endocrine Disorders. Pediatrics. *13*:393, 1954.

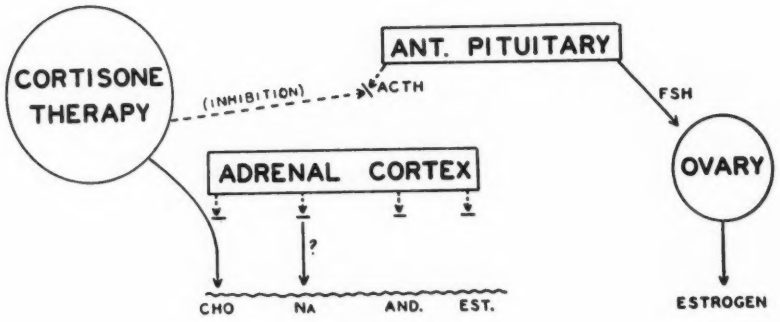

FIGURE 3**

air injection may aid, but this technique may not be conclusive. A therapeutic test with cortisone is the most reliable non-surgical technique for differentiation. Urinary 17-ketosteroids rapidly diminish with steroid therapy in adrenal hyperplasia, but do not respond in adrenal tumor. If, after the therapeutic test, there is a reasonable doubt about the presence of adrenal tumor, exploratory laparotomy should be done.

Treatment

Once the diagnosis of the adrenogenital syndrome, secondary to congenital adrenal hyperplasia, is established, the problem of management presents itself. The cornerstone of modern therapy of this disease is the continuous use of cortisone. The cortisone depresses the ACTH production of the anterior pituitary, which in turn suppresses the production of androgenic steroids. The level of urinary 17-ketosteroids is the best guide to adjustment of dosage. Although steroid therapy is basic, there are many other problems in the management of the patient with this disease.

In the newborn with Addisonian crisis, DOCA and parenteral sodium chloride are necessary adjuncts to therapy. Since any infection or dehydrating illness may throw these patients into crisis, appropriate prophylactic and active therapeutic measures for these intercurrent illnesses are mandatory.

The boy with advanced masculine characteristics and increased size may offer a significant emotional problem. It is important to remember his chronologic age, emotional development and intelligence. Eventually, most other boys will grow to be taller than the patient.

Concerning the female pseudohermaphrodite, the age at which therapy is started is vital. Whether to do plastic surgery on a seven or eight year old child who has been reared as a boy, converting the patient to her true genetic female self, is a problem which cannot be answered didactically. It is necessary to individualize therapy to the entire familial, cultural and psychological situation that exists. Certainly, if the pseudohermaphroditism is recognized at birth, as indeed it should be and the diagnosis of congenital adrenal hyperplasia is established, then the patient should be named and reared as a girl. Needless to say, these girls should be well prepared psychologically for plastic surgery.

Prognosis

Since cortisone therapy, the outlook for these patients has improved dramatically. Recently, a female pseudohermaphrodite, who was treated with cortisone, and who had undergone plastic surgery, was delivered of a newborn infant. The natural history of the disease is such that many succumbed in the newborn period. Those boys who survived went on to be short, muscular men. Those girls who

survived lived either as men or women, short in stature, masculinized with varying types of external genitalia. They were sterile.

With cortisone it is usually possible to weather the storm in infancy, grow relatively normally, and stop the pathologic virilization in both sexes.

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IV. OCCULT HYPERPARATHYROIDISM

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It is the purpose of this paper to review the obscure and bizarre clinical manifestations of hyperparathyroidism. The usual signs and symptoms of this endocrinopathy, such as, bone changes, hypercalcemic symptoms and recurrent renal calculi are well known and will not be considered here. The obscure expressions of hyperparathyroidism, whether due to adenoma or primary hyperplasia, are the same, and will be considered under three categories: 1.) Nephrocalcinosis and Renal Insufficiency, 2.) Peptic Ulcer and Ulcer-Like Syndromes, and 3.) The Burnett[1] or Milk-Alkali Syndrome.

Nephrocalcinosis and Renal Insufficiency

Patients will occasionally present with a symtom-complex of renal insufficiency, manifested by azotemia, anemia, uremic symptoms, generalized pruritis, and polyuria. Surprisingly, there may be minimal expressions of renal damage, scanty urinary findings and often a normal blood pressure. The fortuitous observations of an elevated serum calcium and an increased twenty-four hour urinary excretion of calcium will serve as clues in the recognition of hyperparathyroidism.

A scout roentgenogram of the abdomen may disclose grossly visible calcification of the renal parenchyma (nephrocalcinosis). X-ray examination of the bones may be entirely negative if sufficient dietary ingestion of calcium has been taken to negate the calcium-losing effects of parathyroid hormone. In the absence of osteoclastic bone activity, the alkaline phosphatase level of the serum is normal.

When renal insufficiency is superimposed upon the hyperparathyroid state, the usual biochemical expressions of hyperparathyroidism are masked. In hyperparathyroidism the serum calcium is elevated and the phosphorus depressed, disturbed tubular function tends to elevate the phosphorus and lower the calcium. Moreover, even the Sulkowitch reaction may be misleading, for with the polyuria of renal failure and the loss of tubular concentrating powers, insufficient calcium may be present in a single specimen to produce a strongly positive reaction. Obviously, a twenty-four hour excretion of more than 250 to 300 mg. of calcium is strong presumptive evidence of hyperparathyroidism.

It is a curious and unexplained fact that when patients with hyperparathyroidism develop renal calculi, nephrocalcinosis is not prominent[2]. Conversely, hyperparathyroid patients who develop nephrocalcinosis usually do not suffer from kidney stones. Unfortunately, when nephrocalcinosis and renal insufficiency occur together in hyperparathyroidism, the process is irreversible and ultimately leads to fatal uremia.

Peptic Ulcer and Ulcer-like Syndromes

Guttman[3], in 1934, was the first to call attention to the gastrointestinal expressions of hyperparathyroidism, in a report of four cases of intractable nausea and vomiting in which episodes suddenly appeared and persisted for weeks or months. Guttman astutely pointed out that the gastrointestinal symptoms may so dominate the picture as to suggest duodenal ulcer or acute appendicitis. The association of peptic ulcer with hyperparathyroidism was later emphasized by Rogers and others[4, 5]. In a review of all cases of hyperparathyroidism at the Mayo Clinic[6], it was found that 24 per cent of patients with proved hyperparathyroidism had, at one time or another, evidence of peptic ulcer, or operations on the stomach presumably because of ulcer. An additional 15-20 per cent of patients

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in this series gave a history of ulcer-like symptoms without corroborating x-ray evidence of ulcer. The mechanisms of this association have not been elucidated. Peptic ulcers associated with hyperparathyroidism are notoriously intractable, but respond well to treatment after correction of the hyperparathyroid state.

Burnett's or Milk-alkali Syndrome

Recently Burnett and his co-workers[1] described a syndrome complicating duodenal ulcer that has many features in common with primary hyperparathyroidism associated with renal insufficiency. The observed characteristics in their six patients were: 1.) a history of prolonged excessive milk and absorbable alkali intake in the treatment of ulcer, 2.) hypercalcemia without hypercalcuria or hyperphosphatemia, 3.) normal alkaline phosphatase level, 4.) alkalosis (hypochloremic), 5.) azotemia, 6.) metastatic calcinosis, with ocular lesions resembling band-keratitis, 7.) improvement in the clinical state with a low intake of milk and alkalies.

In a classical paper Walsh and Howard[7] reported, in detail, the ocular lesions which they considered specific for hypercalcemic states, irrespective of cause. Two distinct types of ocular lesions, one in the cornea and the other in the conjunctiva, have been observed, neither of which can be accurately identified without the aid of a slit lamp. This is an important ophthalmological clue in the diagnosis of a hypercalcemic state.

This syndrome of alkalosis and renal insufficiency, resulting from the vomiting of chlorides and the prolonged ingestion of milk and soluble alkalies, appeared sporadically in the literature for a number of years prior to Burnett's report[8, 9, 10, 11].

Since then, Kirsner, Palmer and Humphreys[12] have shown that intense alkalosis alone does not produce permanent renal damage in either experimental animals or human subjects, it seems probable that this syndrome[5] is produced by other etiological factors in association with chronic alkalosis.

With the exception of a few cases, in our opinion erroneously classified as salt-losing nephritis[13, 14], a search of the literature disclosed only four case reports conforming to Burnett's original description[15, 16, 17]. A study of these case protocols leads us, in the light of our own recent experience, to suggest that primary hyperparathyroidism, rather than the so-called Burnett's syndrome, is a more probably diagnosis.

We had under our observation for five years, a patient (case report presented herewith) whom was considered to have Burnett's syndrome, but who, at autopsy, was found to have hyperparathyroidism due to parathyroid adenoma.

Recently, Carpenter and Pautler[18], and Kyle[19] reported cases of hyperparathyroidism with renal insufficiency, identical with ours, which were also confused with Burnett's syndrome. Surgical exploration of the first case (Carpenter and Pautler), with removal of parathyroid tissue, failed to disclose morphologic[21] changes which could account for the biochemical alteration. At autopsy, surprisingly, a large parathyroid adenoma was discovered in the superior mediastinum.

The two cases reported by Kyle illustrate the difficulties in the clear-cut separation of hyperparathyroidism from the milk-alkali (Burnett's) syndrome. Both of Kyle's cases demonstrated the characteristic features of Burnett's syndrome. In one patient, a parathyroid adenoma was removed; in the other, excessive ingestion of milk and alkalies appeared to be the major problem.

CASE REPORT*

This forty-five year old, white male bookkeeper, was first admitted to Mount Sinai Hospital on March 15, 1947, with a twenty-five year history of recurrent ulcer symptoms, manifested by pain-food-relief sequence, frequent black stools and chronic severe anemia. Past history also revealed that in 1929, he had a post-pneumonic lung abscess and empyema, with surgical drainage through the anterior chest wall, and complete recovery. For several weeks prior to this hospital admission, he had been vomiting almost

*Abstracted from "Syndrome of Masked Hyperparathyroidism." Annals of Internal Medicine (in press).

continuously and had been taking large doses of alkalies. Shortly after admission, oliguria was noted and the patient appeared semi-stuporous. The NPN, which had been 68 mg.% on admission, rose to 295 mg.%, the creatinine from 2.7 to 11.5 mg.%, and the CO_2 combining power from 63 to 95 volumes per cent. After the vomiting and bleeding were controlled and the electrolyte balance was restored, the NPN returned to 39 mg.% and the creatinine to 2.3 mg.%. The urine was entirely negative, but the specific gravity was never above 1.015. Because of marked impairment of dye excretion the kidneys or renal pelves were not visualized by intravenous pyelography. The x-ray department reported further that the calcification of the pelvic vessels, seen in so relatively young a person, would suggest some renal disturbance. Retrograde pyelography revealed both renal pelves to be normal with a low lying right kidney. The impression of the medical resident, notwithstanding a normal blood pressure and ocular fundi was: 1.) chronic nephritis with renal failure, uremia, and polycystic kidneys (?), 2.) chronic, bleeding, obstructing peptic ulcer, with alkalosis, dehydration, and secondary anemia. The intern's impression was lower nephron nephrosis on the basis of prolonged alkalosis. Surgical treatment of the "obstructing peptic ulcer" was recommended, which the patient refused; he was discharged five weeks after admission. During the next five years, he was admitted to this hospital sixteen times.

In 1947, the patient was again admitted with the symptoms and findings of a lower lobe pneumonitis, during which period the NPN was markedly elevated but fell as the pneumonia subsided. In 1949, during his several admissions, he complained of profound weakness and of pain in the lower extremities which was relieved by exercise. His ulcer symptoms, pain and burning, which were only relieved by forced vomiting and alkalies, had persisted. During this period, he was in a state of chronic azotemia with an NPN ranging from 100 to 140 mg.%, and chronic hypochloremic alkalosis.

He was advised to take large amounts of salt and to discontinue the alkalies. Because of our inability to bring the chlorides and sodium levels to normal, the recently described syndrome of salt losing nephritis was applied in his case. He was still incorrigible, dosed himself with alkalies, and refused surgery.

In 1949, the ophthalmology department recognized a peculiar form of band-keratitis which they attributed to calcification of the eyeball and the surrounding structures.

In 1951, he finally consented to surgery, and a gastric resection was recommended by the department of medicine. Notwithstanding the high free acid content, a gastroenterostomy was done because of the azotemia. The patient made an excellent recovery and was well until seven months later, when he was again admitted to this hospital, now complaining of substernal oppression on exertion.

These anginoid symptoms were temporarily relieved by blood transfusion. However, they became progressively worse and were no longer relieved by the administration of blood. He now required up to forty nitroglycerine tablets per day. Stellate ganglion blocks afforded temporary relief of the coronary insufficiency, but eventually even this therapy offered no relief, and he was now in a state of intractable *status anginosis*.

He had several additional admissions during the last few months because of gastrointestinal hemorrhages and symptoms suggestive of actual myocardial infarction; although laboratory and electrocardiographic confirmation of an acute coronary occlusion were lacking. He was treated with washed red blood cells, large amounts of sodium chloride, and although vagotomy was considered, it was rejected because of the poor general condition of the patient.

The patient's final admission to this hospital was on January 3, 1953 when he appeared to be suffering from unrelenting substernal pain, sweating and marked apprehension. Generalized twitching and convulsive movements were noted, which were unrelieved by intravenous calcium gluconate. He expired on the following day.

During the last few months prior to his death large quantities of various

opium derivatives were consumed in a vain attempt to secure relief from the agonizing precordial distress. The final clinical diagnosis, as written just prior to the patient's demise was: 1.) chronic renal insufficiency; etiology: a.) chronic alkalosis (vomiting of chlorides and ingestion of alkalies), b.) recurrent hemorrhage, with shock, from a bleeding peptic ulcer superimposed on some pre-existing latent primary renal disease of undetermined nature, possibly chronic pyelonephritis; 2.) generalized calcinosis involving the medium-sized blood vessels, the coronary arteries, the eyeballs, the long bones and the kidneys (nephrocalcinosis)—all resulting from chronic alkalosis plus excessive ingestion of calcium, salts and milk; 3.) recurrent peptic ulcer involving the stoma of a gastroenterostomy; 4.) narcotic addiction in an attempt to relieve *status anginosis;* 5.) terminal pneumonitis.

Summary

The obscure manifestations of hyperparathyroidism have been reviewed and the problems involved in the diagnosis of hidden hyperparathyroidism explored. A case presented is that of "masked" hyperparathyroidism (due to parathyroid adenoma) associated with peptic ulcer, the symptoms and complications of which were confused with the syndrome reported by Burnett, *et al.*

The authors suggest that the symptom complex of hypercalcemia without hypercalcuria or hypophosphatemia, calcinosis, and renal insufficiency in patients with peptic ulcer complications should direct attention to occult hyperparathyroidism as a probable etiological agent.

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V. RATIONALE OF THERAPY IN GOUT

ARNOLD BLACK, M.D.*

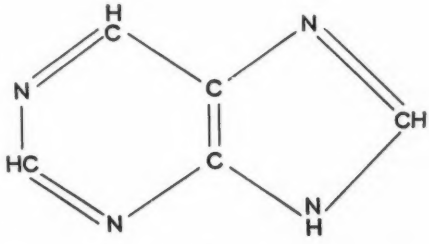
Of the many articles written on therapy of gout, there is general agreement on the principles of the use of colchicine, ACTH or adrenal steroids, and uricosuric drugs. Other problems, especially dietary management, are still a matter of debate. In order to understand the concepts involved and the rationale for the treatment of this disease, it is necessary to appreciate the abnormalities which occur in the gouty individual.

It is generally accepted that all gout is associated with a persistent elevation of uric acid in the plasma. The relationship of this finding to an attack of acute gouty arthritis is not clear. Adrenal cortical insufficiency has been suspected and sometimes implicated but never to an unequivocal degree. Intravenous injections of massive doses of urate will not produce acute arthritis in a normal individual. Similarly, patients with a familial hyperuricemia or a hyperuricemia induced by diseases such as chronic renal insufficiency, polycythemia vera, or chronic leukemia, will maintain persistent elevation of uric acid levels for years without clinical evidence of gout. Therefore, it must be assumed that an unknown factor is the determining influence which designates whether a few additional milligrams of uric acid per 100 ml. of plasma is merely an interesting laboratory abnormality or a potentially severe disease.

Once the individual has had his first attack of acute gouty arthritis, the natural course of the disease is usually exhibited, especially in untreated cases. This takes a rather characteristic pattern of recurrent episodes of acute attacks interspersed with completely symptom-free intervals. The periods of illness gradually grow more frequent and more severe until the individual has reached the stage of chronic gouty arthritis. There is a concomitant deposition of urate crystals in various tissues, some of which are visible in the form of tophi. In addition the patient becomes, rather prematurely, a victim of the degenerative vascular diseases, and it is frequently this involvement, either of the coronary, renal, or cerebral vessels, which causes his demise.

Uric Acid Metabolism in Normal Individuals

Ingested protein material makes up the exogenous source of uric acid. All living tissues contain nucleoproteins, which on digestion are broken down into protein and nucleic acid. The latter, on further hydrolysis, yields purines, pyrimidines, a sugar (d-ribose), and phosphoric acid. A purine is a chemical compound having a double ring structure composed of five carbon and four nitrogen atoms.



Two purines, adenine and guanine, occur in all nucleic acids. By a process of deamination and oxidation the following changes occur:

Adenine ⟶ Hypoxanthine ↓
Guanine ⟶ Xanthine ⟶ Uric Acid

The last stage occurs in the liver by means of an enzyme, xanthine oxidase.

Recent work with isotope techniques has confirmed and more accurately de-

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lineated the source of endogenous purines. It is known that on a purine-free diet, normal individuals will excrete about 300-600 mg. of uric acid daily. This was originally thought to result from the breakdown of cellular nucleoproteins of the body during the normal process of catabolism and replacement. At present, the precursors of these endogenous purines have now been demonstrated to be derived also from very simple substances such as glycine, carbon dioxide, formic acid, and ammonia. They enter into the formation of a compound, as yet not completely identified, which can either be transformed into a simple purine ring, or may be used in the synthesis of nucleoproteins.

Uric acid is present in the body fluids in the form of sodium urate. A small portion of this (4 to 24 per cent; average 16 per cent) is bound to a protein complex. This so-called "bound" uric acid is found to be increased in gouty individuals.

The excretion of urate occurs primarily through the kidneys. As much as 95 per cent of N^{15} labeled uric acid, which has been injected intravenously, has been recovered in the urine within five days[1]. The glomerular filter allows all urate to pass through, but 90-95 per cent undergoes tubular reabsorption. This process serves no known useful purpose and most probably is an atavistic mechanism. Increased excretion of uric acid is produced by partial blockage of reabsorption at the tubular level. This can be effected by certain drugs such as ACTH, adrenal steroids, probenecide, phenylbutazone, salicylates, and cinchophen. A high carbohydrate diet is also helpful. Uric acid excretion is decreased by starvation, exercise, a high fat diet, and drugs *i.e.*, lactate, benzoate, ergotamine, and atropine. Colchicine has absolutely no effect on uric acid excretion. Balance studies have revealed no alteration in urate metablism during the administration of this drug. Because of the small doses therapeutically effective, it has been postulated that there must be some action on an enzyme system. This theory awaits the results of current investigations with isotope labeled colchicine.

The Miscible Pool of Uric Acid

Following the synthesis of uric acid containing N^{15}, an extensive group of experiments were accomplished to establish the concept of a "metabolic pool[2]". Labeled uric acid was injected into individuals kept on a controlled diet, adequate in protein and low in purines. The amount of urate, both normal and isotope labeled, that was excreted in the urine was measured for at least five days. From calculations of the data obtained, it was possible to estimate the total amount of urate present in all body fluids, as well as the rate of turnover of uric acid in the body.

Normal individuals have a miscible pool of uric acid of about 1—1.5 grams with about 50-70 per cent turnover every day. The pool in gouty individuals is much higher, usually at least 5 grams, with some values as high as 30 grams. The percentage turnover rate is slightly lower, but the absolute value in milligrams per day is often much higher.

There are three possible mechanisms causing hyperuricemia:

1. Overproduction
2. Diminished destruction
3. Diminished renal excretion

These theories will be examined very briefly.

Overproduction Theory

The most recent evidence in support of this concept has been presented by Benedict[3]. Glycine tagged with N^{15} was used to estimate the endogenous production of urate. Apparently, gouty individuals synthesize urate and excrete the labeled uric acid in quantities three times as great as normal. In further support of this concept, Friedman and Byers[4] have demonstrated a definite increase in uric acid excretion in young gouty patients, whose kidney function was apparently normal. This would seem to indicate that the person with gout is forming increased amounts of endogenous uric acid and attempting to excrete some of the excess. The above findings have not been adequately confirmed by other investigators to achieve general acceptance.

Diminished Destruction Theory

Conclusions drawn from some N^{15} labeled uric acid experiments, in normal individuals, indicate that the daily endogenous uric acid production is higher than the daily uric acid excretion varying from 110 to 250 mg. This could point toward the existence of some unknown mechanism of destruction of uric acid which in turn might be deficient in gout. A significant amount (47 per cent) of labeled uric acid, when given orally, is metabolized and excreted as urea. However, this is probably due to degradation within the gastrointestinal tract, since parenteral administration of the same material results in 95 per cent recovery of uric acid in the urine[1]. Other authorities have found lesser amounts. The evidence, at present, is not conclusive to indicate that there are other metabolic pathways for the destruction of uric acid in man. No uricolytic enzymes have been found in any tissues.

Decreased Renal Excretion

The enthusiasm about the concept of a renal mechanism in gout is based at present on Berliner's work[5]. This indicated that when normal individuals are given intravenous injections of urate, the clearance of urate will rise with increasing plasma levels. Since gouty patients have these increased plasma levels and are not able to excerete the excess, it is postulated that there is an increased (exaggerated) tubular reabsorption of urate. In other words, the kidney of a gouty individual excretes a normal amount of urate only because of the elevation of the plasma level; if this level were normal, the excretory rate would be diminished.

Certainly, the final word has not been written about this elusive problem, and recognized authorities in the field are of the opinion that conclusive evidence in support of any of the three hypotheses is lacking.

Objectives of Therapy

No matter what theory we follow, it must be assumed that the disturbance in gout is somehow related to the excess of uric acid and any attempt at therapy would have to be directed toward the correction of that abnormality. The broad objectives of therapy must include the following:

1. Alleviation of acute attack
2. Prevention of recurrences
3. Prevention of tophus formation and dissolution of existing tophi
4. Prevention of degenerative vascular disease.

The drugs most useful in the acute attack are colchicine, ACTH, the adrenal steroids, and phenylbutazone. There is no scientific reason for using colchicine, except the empirical observation that it is highly effective in reducing symptoms in the majority of cases. ACTH and adrenal steroids are used for acute gout, because of their "anti-inflammatory" action. The mechanism of action of phenylbutazone is probably of a similar nature, since a significant uricosuric effect requires doses of 600 mg. daily[6], while an attack will frequently be aborted with smaller doses. In general, the treatment of an acute attack of gout is accomplished by drugs whose fundamental mode of action is unknown.

The prevention of recurrence can be approached with the assumption that hyperuricemia is the basic disturbance and the uricosuric drugs, while correcting this chemical abnormality, will also alter the clinical picture. This concept is not completely true, because colchicine is frequently effective in aborting a severe attack if administered in the premonitory phases. In addition, it helps prevent the flareups which frequently occur in the early months of probenecide therapy. In any event, the most effective uricosuric drug known is probenecide, and a recent report[7] is quite enthusiastic—even to the extent of comparing its action to that of insulin in diabetes. Prolonged administration will cause a significant fall in the serum uric acid level, a decrease in the size of the urate pool, and even a shrinkage of tophi. Whether this is the complete answer remains to be seen.

Other uricosuric drugs include salicylates, phenylbutazone, and cinchophen.

In cases where probenecide cannot be tolerated, salicylates are effective if used in adequate doses, and on an intermittent basis. For some unknown reason, constant administration loses its effectiveness after a period of time, but this is regained with brief rest periods. Phenylbutazone had demonstrated a significant degree of toxic reactions to make long term administration rather dangerous. Cinchophen, while generally in disrepute, may occasionally be valuable, since it is felt that most of the serious reactions occurred in patients with rheumatic arhritis and not with gout[8].

The problem of diet is still a "bone of contention" especially with the knowledge of the production of endogenous urate from basic substances other than nucleoprotein. In addition, the question of alcoholic beverages precipitating attacks is also open to discussion. From the practical standpoint the following principles may be observed:

a. Avoidance of agents known to excite attacks in the specific individual.

b. Following a moderately low purine diet. This is a compromise between a rigid low purine diet, which is highly unpalatable to the average patient (because it contains little meat), and a normal diet which is high in purines and would add an extra burden to an already overloaded system.

c. There is no controversy about the use of a low fat, high carbohydrate intake, with calory control to keep weight at an optimum level.

The prevention of tophus formation and the dissolution of existing tophi can be accomplished only by potent uricosuric drugs, and at present, probenecide may prove to be an effective agent. The specific results of therapy will have to await adequate evaluation.

Finally, the prevention of degenerative vascular disease is still an unanswered problem. This will be determined when the exact nature of gout is known and treatment has advanced beyond the present stage.

Summary

1. Gout is a disease of unknown etiology associated with a persistent elevation of plasma uric acid and a significant increase in the metabolic pool of urate.

2. Three possible mechanisms may be the cause of hyperuricemia: overproduction, diminished destruction, or decreased excretion. Conclusive evidence in support of any of these is lacking.

3. Therapy in gout should have as its objectives: the alleviation of the acute attack, the prevention of recurrences, the prevention or dissolution of tophi, and the prevention of premature degenerative vascular disease.

4. The relief of the acute attack is accomplished by either colchicine, ACTH, adrenal steroids, or phenylbutazone. The specific mode of action is unknown.

5. All other objectives of therapy may possibly be achieved by prolonged administration of a highly potent uricosuric drug, the best of these at present being probenecide. The total effectiveness of this medication will have to be evaluated over a period of many years.

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VI. CLINICOPATHOLOGIC CONFERENCE

Presented at Mount Sinai Hospital, Chicago, Illinois

DR. E. FREILICH, Chairman DR. M. RAPPAPORT, Secretary

Abstracted by DR. M. EINHORN

CLINICAL HISTORY

First Admission: The patient, a fifty-two year old white female, was first admitted to Mount Sinai Hospital on February 24, 1950 with the chief complaint of severe "knife-like" pain in the left upper quadrant of the abdomen which was of sudden onset. This pain radiated from the left flank to the umbilicus and down the back to the rectum. Frequency was noted, but dysuria and hematuria were absent. There was no associated nausea or vomiting.

Past history revealed that the patient had been treated for osteoporosis for an unknown period of time. A chronic cough, productive of a thick, white sputum, was likewise present for an unknown period. A roentgenogram had been done some time previously and the patient had been told that, "she had a kidney stone." Family history was noncontributory.

Physical examination revealed a small, thin female who appeared to be acutely ill. She was obviously dehydrated and in severe pain. Kyphoscoliosis of the upper thoracic spine was noted. The heart was within normal limits. Blood pressure was 138/68 and the pulse rate was 84 per minute. The lungs were clear to auscultation and percussion. The abdomen was moderately distended and the pattern of distended bowel loops was visible. No peristaltic waves were noted and bowel sounds were absent. There was marked tenderness in the left upper quadrant and the Murphy tap was positive on the left. Rectal examination was negative; examination was otherwise negative.

One week after admission, on cystoscopy, a small stone was found in the middle lower third of the left ureter, and a ureterotomy was performed. She was discharged three days later in good condition.

Second Admission: The patient reentered Mount Sinai Hospital on December 28, 1952 with the complaint of severe, constant pain in the right flank, radiating to the right lower quadrant, for the past day. This was accompanied by nausea and vomiting; other urinary symptoms were absent.

Physical examination revealed a poorly nourished, white female who was acutely ill. Blood pressure was 130/70 and the pulse rate was 72 per minute. Diffuse moist rales were present throughout both lung fields. The heart was enlarged to the left, revealing an aortic configuration. A grade III systolic murmur was present over the apex. The abdomen was soft with slight muscle guarding in both the left lower quadrant and the right upper quadrant. No masses were palpable. Examination was otherwise negative.

An intravenous pyelogram and a cystoscopic examination revealed a translucent calculus at the right ureteropelvic junction. The patient was discharged one week after admission, with a follow-up scheduled on an out-patient basis.

Third Admission: The patient was rehospitalized two days following discharge when she noted colicky, nonradiating pain in the right flank.

Physical examination revealed tenderness at the right costovertebral angle and a few rales throughout both lung fields. Examination of the heart was negative.

A right pyelotomy was performed, and a stone at the ureteropelvic junction was removed. The patient's post-operative course was uneventful and she was discharged January 20, 1953, two weeks after admission, in good condition.

Fourth (Final) Admission: The patient re-entered Mount Sinai Hospital on May 22, 1954 (four years and three months

after the first admission), with the complaint of acute, severe pain in the left upper quadrant, accompanied by chills, vomiting, and backache.

Physical examination revealed a poorly developed, poorly nourished, white female who did not appear to be acutely ill. A kyphosis with right scoliosis of the upper thoracic and cervical vertebrae was noted, as on the first admission. Blood pressure was 140/70 and the pulse rate was 78 per minute. Examination of the lungs revealed diminished to absent breath sounds over the left lung and a few rhonchi over both lung fields. A systolic murmur was heard over the apex and aortic area. The abdomen was slightly distended, but examination was otherwise negative.

In view of the laboratory findings, surgery was performed on June 19, 1954, at which time a thyroidectomy, together with the removal of a nodule from the upper mediastinum was done. The immediate post-operative course was satisfactory. However, in the evening the patient became restless, complained of pressure in the neck and had difficulty in breathing. Cyanosis was absent. She frequently expectorated a thick, mucous sputum. At about 12:30 A.M. she suddenly became restless, her respiratory movements became shallow, and the pulse thready and rapid. The patient expired at 2:00 A.M. on June 20, 1954.

Discussion

*Dr. S. Sorosky**: The history mentions treatment for osteoporosis, which occurred before our contact with the patient. When I first saw this patient, it was for an episode of renal colic. She gave only vague information as to any specific therapy given for osteoporosis. During the interval between the first and second admission to the hospital, the patient passed renal stones spontaneously. I was called to her home when she showed the typical symptomatology of renal colic. X-rays of the K.U.B. tract, and the I.V. pyelograms revealed that the stones had passed spontaneously. Only on her second admission to the hospital did we become suspicious of the true pathology. At that time there was a calculus in the right renal pelvis. The patient also stated that her posture was becoming progressively worse, *i.e.*, the kyphoscoliosis had become more pronounced. The patient refused surgery at this time, and left the hospital to take care of urgent personal matters. However, because of the severe pain she re-entered this hospital a few days later.

In the past, because of the possibility of a parathyroid adenoma, the patient was urged to enter the hospital for a complete work-up, and possible exploration of the neck. However, because of frequent episodes of renal colic, the patient delayed this procedure. She stated, "that she wanted to wait and build herself up." Exploration of the neck was finally consented to, because of the extreme weakness and the weight loss, which had occurred in the three to four months prior to her final admission. Her average weight was about ninety-four or ninety-five pounds; on entry to the hospital, it had dropped to eighty-one pounds. She stated that "she could hardly get around and felt extremely weak." On her second admission to the hospital, the B.M.R. was a plus 13; there was no weight loss or weakness present. However, with the third admission, the B.M.R. was elevated (plus 33), and the radioactive iodine studies were compatible with a hyperthyroid state. Apparently, the patient developed hyperthyroidism a few months prior to exploration of the neck.

*Dr. L. Cardon***: My thoughts in this case, I think, are best and most briefly described in the consultation note which was written on the 27th of May: "The history of multiple recurrent bilateral renal calculi, osteoporosis, skeletal deformity, elevated serum calcium and alkaline phosphatase, reduced serum phosphorus, and a markedly increased urinary excretion of calcium (strongly positive Sulkowitch test) on a low calcium diet, makes the diagnosis of hyperparathyroid adenoma or hyperplasia practically a certainty, and indicates surgical exploration of the neck. Finding and removing an adenoma will not cure the

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LABORATORY DATA

Blood count:	RBC	WBC	Hgb. Gm.	Hgb. %	C.I.	Stabs	Segs	Bas	Lymphs	Monos	Eos
1st Adm.											
2/24/50	4.63	12000	9.8	62.8	.67	2	81	1	12	4	
2nd Adm.											
12/29/52	4.50	8850	13.8	84.6	0.94		62		26	11	1
3rd Adm.											
1/8/53	4.20	19200	12.5	80	0.97	2	88		8	2	
1/10/53	5.09	10200	15.6	99.8	1.0	6	65		25	2	2
4th Adm.											
5/24/54	4.8	11500	12.5	80	0.83	8	52	1	28	5	6
	(+anisocytosis; 1+ hypochromia with tendency to be macrocytic)										
6/14/54	5.7	9350	14.8	95	0.91	11	57	1	24	7	

Urinalysis:	Color	React.	Sp.Gr.	WBC	RBC	Alb.	Blood Sugar		Epith. Cells	Crystals	Casts	Phos. Urates	Mucus
1st Adm.													
2/27/50	amber	6.0	1.015	2-3	0	Tr.	0	0	rare	amorph.	0		
3/2/50	amber	6.0	1.021	1-2	0	Tr.	0	0	occ.	ca. oxal.	0		
2nd Adm.													
12/29/52	amb. cldy.	5.5	1.020	10-12	100-150	1+	1+	0	few		0	0	
1/2/53	Rt. ureter:			0	14-16		2+				0	many pres.	
	Lt. ureter:			0	0		0				0	" "	
	Bladder:			0	200-300		2+				2gm.	" "	
3rd Adm.													
1/9/53	lt. amb. cldy.	7.0	1.013	rare	25-30	Tr.	1+	1%	rare				
1/13/53	" " "	5.5	1.015	1-2	6-9	Tr.	Tr.	0	few	few ca. ox.			
4th Adm.													
5/24/54	pale yellow	5.5	1.018	3-4	0-1				occ.	num. ca. ox.			1+

	Total volume	Phosphatase mg%	Phosphatase mg/24 hrs.	Calcium mg%	Calcium mg/24 hrs.
4th Adm.					
5/28/54	1110 cc.	17.2	191	20.0	222.0
5/29/54		46.5	357	27.7	214
5/30/54	1680	16.8	310	23.5	394.8
6/1/54	1075	11.3	121	18.9	204.1

Blood Chem:	Gluc.	UreaN	Uric acid	Alk. Phos.	Chol.	Esters	T.P.	Alb.	Glob.	A/G	Calcium mEq/L	Calcium mg%	Ionized mEq/L	%. P. mg%	%(cal.)	Phosphorus mEq/L	Phosphorus mg%
2nd Adm.																	
12/29/52	82	15.5	7.0	32	200	68%											
1/5/53							6.3	4.6	1.7	2.7	6.6	13.2	3.7	7.7	6.3	1.9	3.2
3rd Adm.																	
1/12/53	98	19.4	7.2	31.0			6.3	4.2	2.1	2.0	(amylase 75)						
1/20/53											6.8	13.6	2.74	5.48	6.3		
4th Adm.																	
5/24/54													3.3	6.6	7.2	1.53	2.63
5/28/54				66.5													

Hematology 4th Adm. 5/27/54 Sed. rate (uncorrected) 30; hematocrit 46; prothrombin time 15 sec. (control 13 sec.) clotting activity 73%

present deformities, but may prevent the progression of the disease and the formation of new calculi. The kyphoscoliosis of the upper thoracic spine is associated with hyper-resonance to percussion and diminished to absent breath sounds over the left lung, while the breath sounds over the right lung are normal. There is a numular mucopurulent sputum."

The patient had lost much weight, and although there was no clinical evidence to suspect hyperthyroidism, a B.M.R. and R.A.I. (radioactive iodine absorption) test were recommended. In addition, we advised a 24 hour urine for quantitative calcium and phosphorus excretion on a low calcium diet and surgical exploration of the neck for parathyroid adenoma or hyperplasia. As you know, the B.M.R. and the R.A.I. test subsequently proved to be elevated so that it became apparent that this patient had both, hyperparathyroidism and hyperthyroidism. Under ordinary circumstances, if hyperthyroidism alone had been present, it is likely that we would have attempted to treat it without surgical exploration of the neck; particularly in view of the patient's deformity and the consequent difficulty that might be expected with surgery. But because of the parathyroid adenoma, and the hyperparathyroidism which obligated exploration of the neck, it was thought best to prepare the patient for both thyroidectomy and parathyroidectomy, and this was done.

Bacteriology: **Urine Culture:** 2nd Adm: 1/3/53 Right and left ureter and bladder: No growth.
Sputum: 4th Adm.: 5/27/54 No acid fast bacilli; numerous pus cells.
Culture: mixed flora; predominantly beta strep. and non-hemolytic staph. aureus.
6/2/54 Numerous pus cells. Mixed flora predominant, Gram. pos. cocci; few mycelial elements; no acid fast bacilli.
Culture: mixed normal flora.
6/4/54 No acid fast bacilli. Gram stain: mixed flora predominantly gram negative cocci. Many pus cells.
Culture: rare beta hemol. strep. Neisseria catarrhalis predominant.
6/7/54 Gram: mixed flora. Many pus cells. Predominant Gram. pos. cocci in pairs and chains. No yeast cells or mycelial segments.
6/11/54 No acid fast bacilli. Gram: mixed flora, innumerable Grm. + cocci, chains; moderate gram. neg. diplococci with a few gram neg. rods.
Culture: mixed flora; predominantly D. pneumoniae.
Feces for routine exam: 4th Adm. 6/2/54 Blood, gross: negative; occult 1+
6/4/54 Blood, gross: negative; occult 1+

Bact. & Paras. Stool: 4th Adm: 6/2/54 No micro-organisms commonly considered as pathogenic were grown.

Sulkowitch test: 2nd Adm. 12/30/52 Moderately positive
12/31/52 Strongly positive
1/2/53 Moderately positive
1/5/53 Strongly positive
4th Adm. 5/24/54 Heavily positive

Serology: 1st Adm. 2/24/50 Kline, Wassermann (Kolmer)Neg.
2nd Adm. 12/31/52 Kahn, Kline, Wassermann:Neg.
3rd Adm. 1/10/53 Kahn, Kline: Negative
4th Adm. 5/25/54 Kahn, Kline: Negative

Isotope: 4th Adm. Thyroid tracer study: compatible with a hyperthyroid state.

Basal metabolism: 2nd Adm. 1/5/53 Plus 13-1/2%
4th Adm. 5/27/54 Plus 32%
6/11/54 Plus 33%
6/11/54 Plus 28-1/2%
6/17/54 Plus 22%

ECG: 4th Adm. 5/24/54 Low voltage; compatible with hypothyroid state.

X-rays: 1st Adm. 2/25/50 KUB: Summary: (1) suggest returning the patient for repeat films after she has been cleaned out. (2) no evidence of a ureteral calculus is seen at this time.
2nd Adm. 12/30/52 Chest:Summary: some pulmonary congestion is noted. There is suspicion of a mass behind the heart shadow. Follow-up studies advisable.
KUB: Summary: Calculus is noted in the right kidney region. Another calcification is observed in the pelvic region characteristic of fibroid.
I. V. P.: A renal calculus is noted within the right kidney. Marked osteoporosis of the spine and of the pelvis.
1/2/53 Retrograde: Summary: Large renal pelvic calculus of the right side. Right hydroureter. Hydropyelitis, left, spastic calyces on left. Mass in the pelvis, with pressure effect on the ureter. Small calcified densities in pelvis are possibly due to calcified myoma of the uterus. Osteoporosis of the pelvic bones and vertebrae. For the above mentioned shadow behind the heart, an over-penetrating film of the chest is necessary for exact evaluation.
4th Adm. 5/28/54 Abdomen-colon, pelvis; Lumbar spine and chest: the case is characterized by marked osteoporosis; kyphosis; there is wedging of the vertebrae; some evidence of heart failure; large pulmonary arteries and markedly curved descending aorta. the large bowel shows no pathological changes.
6/8/54 Mediastinum-trachea: Summary: an enlarged heart is noted. Normal position of the trachea is seen. There is no pathology in the soft tissues.

Path. report: 3rd Adm. 1/8/53 Diagnosis: Renal stone.

Dr. H. Isaacs†: The one electrocardiographic tracing that we have showed (remember, this patient was 52 or 53 years old) low voltage and an elevation of S-$T_{1,2,3}$ with upright T waves. The T was up in $_{a}V_{L}$ and $_{a}V_{F}$. The rate was very slow, and the P-R interval was normal. The V leads were normal. When we have low voltage in an electrocardiogram, we think along certain lines. It may be due to myxedema, pericardial effusion, severe myocardial degeneration, generalized anasarca and occasionally low T waves are associated with electrolyte disturbances, especially hypopotassemia. I'll admit that after reading the history and findings, more information can be derived from the EKG. The thought in mind was that perhaps the low T waves may also be due to hypopotassemia. There was a peculiar paradox in this case. One, was that the basal metabolic rate was plus 33. Usually, the electrocardiographic tracings of thyrotoxicosis show a definite tachycardia and a high voltage. This was not present here. No irregularities of the pulse were pres-

†Chairman, Dept. of Medicine, Mt. Sinai Hospital; Professor and Chairman, Dept. of Medicine. The Chicago Medical School.

ent, and the essential finding of the electrocardiogram was low voltage with a slow pulse. So the peculiar paradox lies between the electrocardiogram, the thyroid tracer, and the basal metabolism. Perhaps, in summary, the low voltage T waves may be due to a low blood potassium, which also might have something to do with the sudden termination.

Just one or two other points should be brought out, especially for the clerks and not for the general audience. First, I believe that Dr. Cardon's diagnosis of hyperparathyroidism is correct. Second, kidney punch tenderness, or Murphy tap, is not pathognomonic of renal stones. It can occur with any kidney disease. I've elicited it in pyelitis, kidney tumors, polycystic kidneys with hemorrhage, *etc.*

The second practical point is that whenever a heart murmur is heard, especially a systolic one at the apex, plus a history that sounds like a renal colic, one must feel that the process is embolic in character, and that the logical diagnosis would be that of a subacute bacterial endocarditis.

*Dr. J. Arendt**: (X-ray findings): Here we have the significant combination of stone disease and osteoporosis; the laboratory data which accompany this picture: the increased alkaline phosphatase, the positive Sulkowitch test, the increasing prominent kyphoscoliosis. All data support the attending physician and Dr. Cardon's convincing diagnosis of either a hyperparathyroid adenoma or hyperplasia, in which we concurred when the question was first raised.

The diagnostic problem in this case, which lends itself to reflection, lies in the recognition of the early phase of the disease; where first, one stone and then another one has to be recognized not as an event of precipitation, but rather as suspicious of hyperparathyroidism.

Multiple stones are found with vitamin deficiencies, gout, steatorrhea, and prolonged bed rest as in the so-called *cast syndrome*. In fact, in the cast syndrome, the stones are frequently combined with

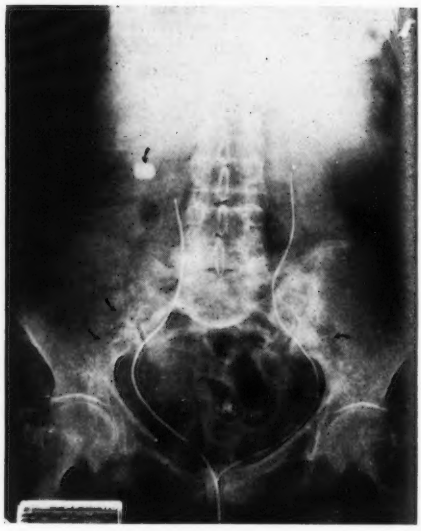

FIGURE 1

Retrograde pyelogram showing a calculus in the right renal pelvis. Marked osteoporosis of the bony pelvis is also seen.

marked osteoporosis. Largely due to Albright, the high incidence of stones in hyperparathyroidism has become common knowledge.

As to osteoporosis, as a roentgenological phenomenon, we should be aware that this is a normal process of aging and may even occur in a woman of this age with premature senescence. In fact, it is found in the post-menopausal type of osteoporosis; the kyphoscoliosis is simply an expression of the caving of the vertebrae and the degenerative changes in the intervertebral discs.

To make the diagnosis of osteoporosis even more difficult, one should be aware that the differentiation between osteomalacia and osteoporosis is not always an easy one, at least not on x-ray films. There is enough calcium deficiency with deformity here to seriously consider, that we may be dealing with osteomalacia as well as with osteoporosis. Osteomalacia is not the "Chinese disease," but occurs with hyperthyroidism, renal acidosis and dietetic deficiencies. We did not, however, seriously entertain the differential diagnosis of osteomalacia because osteoporo-

*Chairman, Dept. of Radiology, Mt. Sinai Hospital; Associate Professor of Radiology, The Chicago Medical School.

sis is so much more common, and there were no particular features noted in this type of "decalcification." Although there was no evidence of a pelvic deformity, course trabeculation with many stress lines were found in the pelvis (*Figure* 1); an expression of marked osteoporosis. X-ray films taken showed kidney stones first on one, then on the other side. Slight deformed lumbar vertebrae with more marked changes were in the thoracic area (*Figure* 2), together with biconcave impression, flattening and loose trabeculation with some effacement of the vertebral outlines. No cystic changes or insufficiency fractures were seen.

The chest film (*Figure* 3) shows the lungs transparent and emphysematous; the pulmonary arteries are prominent and widened on both sides, suggestive of a *cor pulmonale*. However, in view of the flattening of the lower thoracic diameter and the marked tortuosity of the decending aorta, considerable displacement and rotation of the heart had taken place. No evidence was seen of a hyperparathyroid adenoma, in the form of a tumor of the mediastinum. On later films,

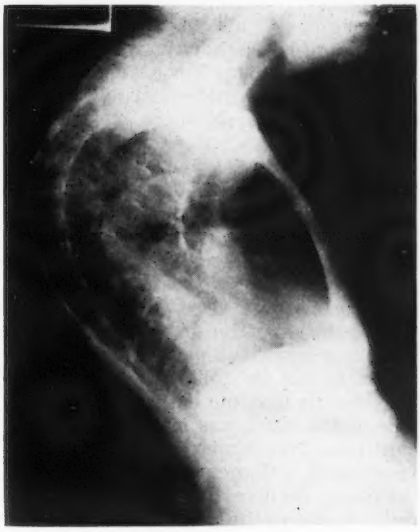

FIGURE 2

Roentgenogram of the chest (lateral view) showing the extreme degree of thoracic kyphosis and wedging of the thoracic vertebrae.

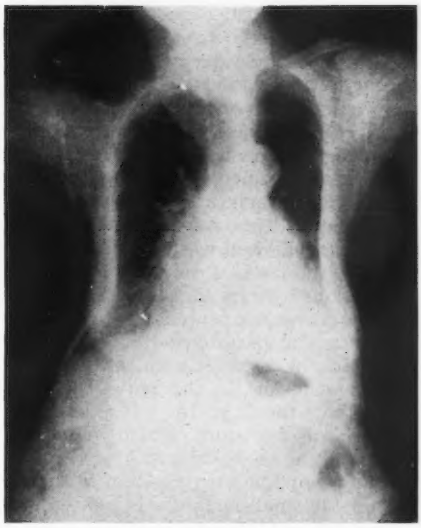

FIGURE 3

Roentgenogram of the chest (A-P view) illustrating the cardiomegaly with rotation of the heart, pulmonary congestion, and a markedly curved descending aorta.

an infiltration on the left lung base was found, together with diminished aeration and probable atelectasis in the right lung base.

The colon was normal. An upper G-I series was not done.

*Dr. L. Aries**: Von Recklinghausen's disease or hyperparathyroidism was first operated by Mendel in 1926. The first recorded case in which a parathyroid adenoma was removed was in 1926. From 1926 to 1942 there were only fourteen cases reported in the literature. In 1945 when I reviewed the literature, there were forty-five cases on record. We've had only one proven case in this hospital up to the time that this patient was operated upon and at that time, the patient had a very classical history with definite findings. At that time, we were able to feel a small pea-sized mass in the right side of the neck; histologically it was a parathyroid adenoma.

* Chairman, Dept. of Surgery, Mt. Sinai Hospital.

This patient had a short neck, and it was very difficult to feel any nodules in the neck. Surgery was performed through the classical "low-collar incision," and after a careful exploration with close collaboration with the pathology department; each nodule of the parathyroid was examined, by frozen sections, to see if an adenoma were present. None were found. This was somewhat disappointing, and when we were about ready to close the neck, I felt that one more look further down in the anterior mediastinum was warranted. Approximately 18 per cent of parathyroid adenomas are found in the mediastinum, either anterior or posterior. In this patient a small nodule was found on the left side of the anterior mediastinum, which could not be seen in the neck when looking through the incision; but on palpation with the finger, this small nodule was located and brought up into the neck; its blood supply was easily controlled by a small clamp, and we were able to identify it immediately by frozen section, as a parathyroid adenoma. We were very pleased because this "clinched" the diagnosis. Clinically, it was very definitely a case of a parathyroid adenoma. The patient was watched carefully for signs of tetany; because in these patients, after removal of an adenoma, the normal parathyroid tissue becomes depressed and on removing the adenoma, it takes several days for the normal parathyroids to become active and take over the function that is normally theirs. However, here, on careful observation the patient developed no tetany and had a very smooth post-operative course the first day. However, from the clinical history you know what followed.

Dr. A. Luisada‡: This patient had three sets of disturbances and diseases. One is below the diaphragm, and in the bones, and I shall leave it up to you. The second is a thyroid and parathyroid condition with formation of the nodule in the upper mediastinum. The third is *cor pulmonale*, a disturbance which is probably connected with the kyphoscoliosis. I don't know how long this kyphoscoliosis had been going on. (Voice: "five years"). Five years is a rather long time. We know that these patients usually develop a syndrome of chronic *cor pulmonale* which is due to rigidity of the chest and the purely diaphragmatic type of respiration. Now, in favor of this, we should note that there was no polycythemia and no definite changes of the electrocardiogram, *i.e.*, right axis deviation and/or right ventricular hypertrophy. However, these data are only compensatory phenomena. Some patients are unable to develop polycythemia or show evidence of right ventricular hypertrophy.

In the interpretation of some of the physical data like the systolic murmur and electrocardiographic findings, we should consider that here the heart is not in the correct, normal position within the chest. Therefore, in these patients, it is extremely difficult to interpret murmurs or even the cause of a dulness. For example, I wonder how much of the dulness found in the left chest posteriorly was due to a displaced and rotated heart. If it had developed and then disappeared, it may have been due to the lung, but I don't know if this was the case. The same thing is true for the interpretation of some X-ray data. For example, I have the impression that actually, as Dr. Arendt pointed out, there was a large pulmonary artery. However, we should remember that, occasionally, rotation or displacement of the heart accentuates the normal curvature of the pulmonary trunk and the stems of the pulmonary artery, which are usually covered by the cardiac shadow. Now, in the electrocardiogram there are two points which are significant. The first one is that, in the chest leads, the pattern of the right ventricle can be followed down to V_4. This means that the entire anterior surface of the heart was made by the right ventricle. This can be due to either right ventricular enlargement or rotation of the heart. As here, there may be a severe rotation due to the kyphoscoliosis; therefore, it is difficult to explain the changes only on the basis of right ventricular hypertrophy. There was no inversion of the T wave in the V_1 or V_2, a change fre-

‡Director, Division of Cardiology, Mt. Sinai Hospital; Associate Professor of Medicine, The Chicago Medical School.

quently found with right ventricular "strain." There were changes in the T waves, though: In V_1 and V_2, a tall, thick T wave followed by a deep and sharp negative phase. This is frequently found whenever there is enlargement of the right ventricle. This lesion could be due to the effect of the kyphoscoliosis on the heart. A systolic murmur is common in kyphoscoliosis and is very common in chronic *cor pulmonale*. It is usually due to eddies which form in the enlarged pulmonary artery, but the transmission of the murmur may be atypical, due to the different positions of the heart in the chest. I don't know the cause of the systolic murmur, I just want to point out that if there were some deficiency in the oxygenation of the blood (we don't have pulmonary functions test or oximetry to prove it), it would have been dangerous for such a patient to receive certain sedatives and narcotics, especially morphine. We know that, in chronic *cor pulmonale*, morphine treatment may be followed by sudden death. It is justified, then, to ask whether the sudden death of this patient was not due to some effect of the usually harmless sedatives and narcotics. It should be added that surgery of the upper mediastinum is always dangerous and may occasionally lead to death.

*Dr. M. Kirshen**: The facts brought out by Dr. Luisada are known: patients with kyphoscoliosis are extremely sensitive to narcotics and, on occasion, even a small dose of morphine may produce sudden death. In the case presented here, another factor may have been of importance. However, it is difficult to say to what extent this factor was responsible for the respiratory difficulties that this patient experienced post-operatively.

In every case of hyperparathyroidism in which a hyperplastic gland or a tumor of the gland has been removed, some symptoms of tetany may be expected after surgery. But in cases in which the condition persisted for a long period of time a type of tetany, called "bone hunger tetany" by Albright, may develop. This results from a rapid remineralization of the skeleton and can lead to a sudden and severe depletion of calcium in the serum which requires aggressive therapy in order to prevent laryngospasm, severe respiratory difficulties, and death from anoxia.

The reported dose of calcium used in this case was 2 grams in the 24 hours post-operatively, but some severe cases may require up to 20 gm. of calcium per day along with large amounts of Dihydrotachysterol or Vitamin D.

One has to consider the fact that the manipulation of the thyroid in the course of the parathyroid gland dissection may have produced a temporary paralysis of the vocal cords, which in conjunction with the laryngospasm, due to calcium depletion, may have led to catastrophic consequences in a patient in which there was an already impaired gas exchange of the lung, due to long-standing kyphoscoliosis.

*Dr. H. Rappaport***: My first contact with this patient occurred at the time of operation when Dr. Aries asked the Pathology Department to check several nodules which he removed from the vicinity of the thyroid gland by frozen section. Since none of these presented the structure of parathyroid tissue, the upper mediastinum was explored and a node removed which showed the gross and microscopic characteristics of a parathyroid adenoma. It measured 1.5 x 1 x 0.3 cm. and weighed 0.35 grams. On microscopic examination (*Figure* 4), it was composed mainly of chief cells; in some areas there was considerable variation in size and shape. This was interpreted as a true adenoma of the parathyroid gland rather than hyperplasia. The thyroid, which was removed at the same time, showed a nodular goiter with focal areas of hyperplasia consistent with hyperthyroidism.

Post-mortem examination revealed the characteristic bone changes of hyperparathyroidism, particularly in the flat bones. Section of the skull showed *osteitis fibrosa* (*Figure* 6), with complete replacement of the marrow by fibrous tis-

*Attending, Mt. Sinai Hospital; Associate Professor of Medicine, The Chicago Medical School.

**Pathologist, Mt. Sinai Hospital; Associate Professor of Pathology, The Chicago Medical School.

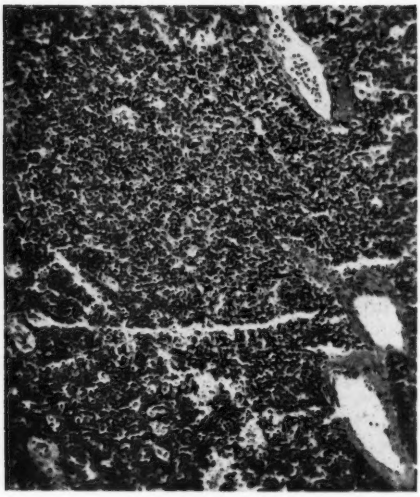

FIGURE 4
Parathyroid adenoma composed entirely of Chief cells.

sue and marked destruction of bone, which was manifested by the presence of moth-eaten bone spicules adjacent to which numerous osteoclasts were present (*Figure* 7). In addition, there was also new bone formation characterized by the presence of osteoid tissue lined with rows of osteoblasts. This increased osteoblastic activity can be correlated with the high serum alkaline phosphatase which was found in this patient during life. In the vertebrae, only a few such areas of fibrosis were found, with marked thinning of the bone spicules and a reduction in their number. They were separated by a very congested bone marrow. The kidneys showed nephrocalcinosis, manifested by focal areas of calcification in the papillae and deposition of calcium in collecting tubules. It is worthy of note, that the kidneys showed no other pathological findings in spite of the history of nephrolithiasis and urolithiasis. On the basis of the findings, thus far discussed, the clinical diagnosis of hyperparathyroidism could be confirmed. However, the problem of the rapid demise after surgery still remains unanswered. The question arose whether this patient may not have had a sudden drop in serum calcium following surgery. Through the foresight of Dr. Cardon, who called this possibility to our attention, we were able to obtain a fairly reliable post-mortem serum calcium level—which was still elevated. Moreover, since the patient did not have the signs and symptoms of tetany, it was felt that on the basis of the post-mortem and ante-mortem blood chemistry studies, plus the clinical findings, acute hypocalcemia could not be eliminated as the cause of death. However, there was an explanation for terminal episode. On opening the thorax, the right lower lobe was completely collapsed. Examination of the bronchial tree revealed that the bronchus leading to the right lower lobe was completely obstructed by a mucopurulent plug. While massive collapse of several pulmonary lobes is a known cause of post-operative death, it would be difficult to explain this situation on the basis of the collapse of a single lobe. However, further examination of the lungs revealed that the left

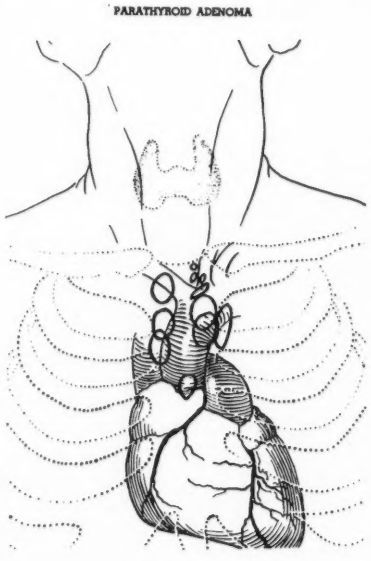

Figure 5 †

† Diagram of position and size of parathyroid adenomata recovered from the anterior mediastinum. Taken from Cope, O.: Surgery of Hyperparathyroidism: the occurrence of parathyroids in the anterior mediastinum and division of the operation into two stages. Ann. of Surgery. *114*:706-733, No. 4. Figure 2, 1941. (Courtesy of J. B. Lippincott Co.)

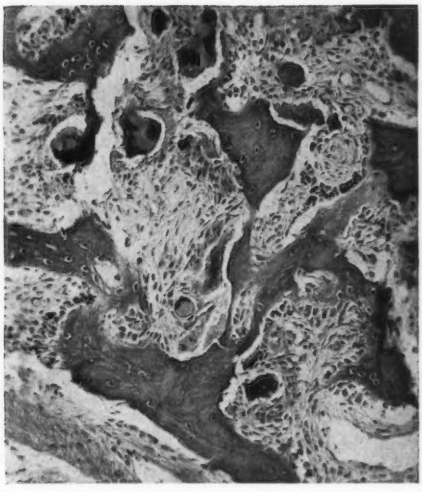

FIGURE 6

Skull—*Osteitis fibrosa cystica.* H. & E. stain x 150.

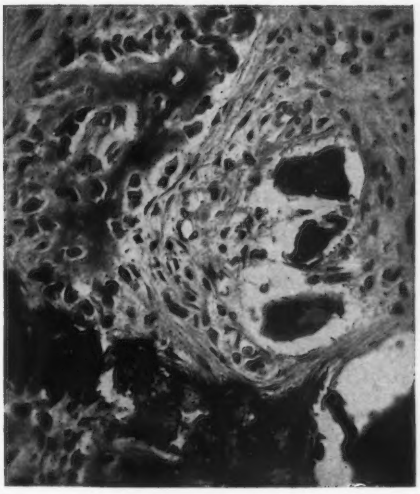

FIGURE 7

Osteitis fibrosa cystica showing bone desruction with oesteoclastic activity in lower part and new bone formation with osteoblastic activity in upper portion.

lower lobe showed an old suppurative process which had led to complete destruction of the pulmonary parenchyma. This lobe was composed almost entirely of dilated bronchi, containing a large amount of mucopurulent material, which apparently were the source of the mucopurulent plug in the right lower lobe. Microscopic sections from both upper lobes showed both gross and microscopic evidence of emphysema. It is obvious that the functional capacity of the two emphysematous upper lobes must have been even further reduced by the presence of kyphoscoliosis. In addition, the right middle lobe showed evidence of broncho-pneumonia. For all practical purposes then, the only portion of the lung which was functioning well at the time of and shortly after surgery, was the right lower lobe, and with its collapse, there was simply not enough functioning pulmonary parenchyma left to keep this patient alive. The only other pertinent finding was a slight enlargement of the heart, which weighed 310 grams as compared with the normal of 270 grams for a patient of this size. The classical finding of *cor pulmonale*, such as a hypertrophied right ventricle, was absent, the right ventricular wall measuring only 0.3 cm. in diameter. However, as Dr. Luisada had suspected, the heart was displaced to the left, due to the considerable decrease in the size of the left lower lobe of the lung.

Final Pathologic Diagnosis

1. Parathyroid adenoma, anterior mediastinum.
2. Hyperparathyroidism manifested by: (a) osteitis fibrosa, (b) osteoporosis, (c) nephrocalcinosis.
3. Chronic suppurative pneumonitis with bronchiectasis and post-inflammatory atrophy of pulmonary parenchyma, left lower lobe.
4. Massive atelectasis, right lower lobe, due to obstruction of right lower lobe bronchus by a mucopurulent plug.
5. Chronic emphysema, both upper lobes.
6. Bronchopneumonia, right middle lobe.
7. Kyphoscoliosis.
8. Hyperthyroidism.

*Dr. H. Weisberg**: I want to make two points, one is the question of nephro-

*Director of Biochemical Laboratories, Mt. Sinai Hospital; Assistant Professor of Clinical Pathology, The Chicago Medical School.

calcinosis in a patient that had kidney stones. Albright and Reifenstein make a very definite statement that usually, when you find kidney stones you don't find nephrocalcinosis, and if you do find nephrocalcinosis you do not expect kidney stones. Whether the amount of nephrocalcinosis present was sufficient to meet that criterion is something for the pathologist to decide. The important thing in this case, as far as I'm concerned, is that we had a classical picture of a hyperfunctioning parathyroid adenoma. Unfortunately, the patient refused an exploratory operation four years ago, when the diagnosis was first suspected; the complications would not have entered into the picture, but, of course, the final outcome would have been the same due to the destroyed lung. Second, the symptomatology was referrable to both the bone disease and the kidney disease as manifested by renal stones and the generalized osteoporosis of the skeleton. We should remember that most of such cases can, and should, be diagnosed before the actual findings of bone disease with *osteitis fibrosa cystica.* Especially, if you find a patient that has a kidney stone or gravel, he should be investigated chemically; the diagnosis can be made with a high serum calcium, especially the ionized fraction, and the low serum phosphorus. The diagnosis will be made much more often if we keep these points in mind.

SCHOOL NOTES AND NEWS

DR. VOLLAN APPOINTED AS NEW DEAN OF FACULTY

Dr. Douglas B. Vollan

Dr. Douglas B. Vollan has been appointed Dean of the Faculty of The Chicago Medical School, effective April 1, 1955, it was announced by Dr. John J. Sheinin, President of the School.

Dr. Vollan, assistant secretary of the Council on Medical Education and Hospitals of the American Medical Association since June, 1952, brings to his duties at The Chicago Medical School a background of experience in surveying programs of post-graduate medical education.

A native of Chicago, Dr. Vollan is a graduate of Wheaton College. He received his medical training at the University of Illinois College of Medicine and was awarded his M.D. in 1943. Dr. Vollan also attended the School of Public Health at Columbia University, receiving the degree of Master of Public Health in 1952.

A veteran of World War II, Dr. Vollan served in the Navy as a Lieutenant in the Medical Corps from 1944 to 1946.

Dr. Vollan is thirty-four years old. He is a member of the American Public Health Association, the Association of American Medical Colleges and the British Columbia College of Physicians and Surgeons. In addition to his recent duties at the American Medical Association, he has served as consulting secretary of the Inter-American Foundation for Post-graduate Medical Education.

NEW APPOINTMENT TO EDITORIAL BOARD

The *QUARTERLY* takes great pride in announcing the appointment by President John J. Sheinin of Doctor James E. P. Toman to the Editorial Board of the *QUARTERLY*. Dr. Toman has been extremely prolific as an author of scientific articles.

Dr. Jas. E. P. Toman

Dr. Toman, born in Manchester, Connecticut, in 1915, received the degrees of Bachelor of Arts from Clark University in 1937, and Doctor of Philosophy from Princeton University, in 1940. In 1950, he completed his pre-clinical work at the University of Utah College of Medicine.

From 1940 to 1943, Dr. Toman served as Instructor in Physiology at the University of Maryland School of Medicine and the following year held a similar position at the University of Vermont College of Medicine. Between 1944 and 1950, he was Assistant Professor of Physiology at the University of Utah College of Medicine. Dr. Toman then entered private industry, holding the post of neuropharmacologist with Abbott Laboratories from 1950 to 1951; he continues with them as a consultant. In 1951, he was appointed Director of Neurophysiological Research at the Institute for Psychosomatic Research and Training of Michael Reese Hospital.

Besides having written more than eighty scientific papers, he is a member of the Board of Editors of the Journal of Pharmacology and Experimental Therapeutics. He is also a member of the American Physiological Society, Society for Experimental Biology and Medicine, American Society for Pharmacology and Experimental Therapeutics, American Society of Zoologists, American Association for the Advancement of Science, Central Electroencephalography Society, American Epilepsy League, and Sigma Xi.

BOOK REVIEWS

TEXTBOOK OF PHYSIOLOGY edited by John F. Fulton, M.D. Cloth. Seventeenth Edition. 1275 pages and 600 illustrations. Philadelphia and London: W. B. Saunders Company, 1955. $13.50.

This is the 17th edition of a now famous textbook of Physiology, first published in 1905. It is one of the standard textbooks in the field. The present reviewer shall not attempt to evaluate it in comparison with the other major textbooks of physiology; other than to state that it is the most up to date revision of any of them. It is arranged in much the same style as previous editions. Certain sections have been entirely rewritten. These are: Principles of Nervous Activity; Body Fluids and Kidney Function; and Respiration. A new chapter on Acetylcholine and energy transformations in nerve cells has been added.

Perhaps, too great a portion of the book has been devoted purely to the consideration of the nervous system; but, this is a fault only too commonly seen in physiology textbooks, whose greater portions are devoted to the favorite subject of the editorial staff. Totally, this is a well written book; in places, rather difficult to understand for an undergraduate medical student, but providing a sound basis for his future medical knowledge.

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DISEASES OF THE SKIN FOR PRACTITIONERS AND STUDENTS by George Clinton Andrews, M.D., F.A.C.P. Cloth. Fourth Edition. 877 pages and 777 illustrations. Philadelphia and London: W. B. Saunders Co., 1943. $13.00.

The author has brought this well known text up to date by the addition of new material and by "careful tightening and as a sharper focus of the older material." The book is up to date, in both text and references. Greater emphasis has been placed on histopathology and especially on the section on tumors of the skin.

A number of new diseases and syndromes have been added, and the sections and therapy revised.

Recent developments in the biochemistry of melanin formation as well as discussions of the L.E. phenomenon in lupus erythematosus, the Treponema pallidum immobilization test for syphilis, the Kveim test for sarcoidosis, the Schiff periodic acid stain for fungi, and the Tzanck technique for cytological examination of vesicular and bullous lesions are included.

Chapters on x-ray and radium therapy and surgical procedures emphasize all pertinent knowledge available. For the specialists in the field the sections on depth dose and back scatter values obtained from the newer beryllium window x-ray therapy tubes, therapy with contact tubes, and thorium X solution are discussed. Improvements have been made in the format and typography.

The book is profusely illustrated. This book is highly recommended.

David M. Cohen, M.D.

FUNDAMENTALS OF ANESTHESIA edited by a Consultant Committee of the Council on Pharmacy and Chemistry of the A.M.A. Cloth. Third Edition. 279 pages and 89 illustrations. Philadelphia and London: W. B. Saunders Co., 1954. $6.00.

The third edition of this popular text has been thoroughly revised by a Chicago committee. Although written in outline form, the first 70 pages are devoted to the Physiology of Respiration; neuropharmacology of inhalants used; and the pre-operative care of the patient. The section dealing with the principles of chemistry and physics is exceptionally well written giving a brief, concise description of the mechanisms involved. The illustrations are diagrammatic and are highlighted by obvious notations. The use of bold type, as footnotes, to connotate various "pearls" of anesthesia are rewarding, both to the reader and the publisher. Obstetrical procedure is covered under "Special Applications;" technique and complications are fairly well covered; however, the important fact that caudal analgesia may delay the second stage of labor is not emphasized. Complications are discussed as a separate chapter—the main emphasis being placed upon prophylaxis.

The form of this text makes any section readily available to the reader; hence this edition is recommended to the surgical resident and to the anesthetist.

H. A. B.

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THE SURGERY OF INFANCY AND CHILDHOOD by Robert E. Gross, M.D., D.Sc. Cloth. 1000 pages and 1488 illustrations. Philadelphia and London: W. B. Saunders Company, 1953. $16.00.

This is probably the most comprehensive book written on this subject. It contains 69 chapters, which cover a remarkably wide range of topics, ranging from such general subjects as Obstructive Jaundice in Infancy to such highly specific ones as Congenital Atresia of the Intestine and Colon, and Ureterocele. All of these are completely discussed, being handled from the aspects of embryology, pathology, diagnosis, and therapy. This latter aspect, particularly, is discussed in detail with more than adequate visual illustration of the techniques involved.

Of greatest value are the introductory chapters which discuss: Preoperative and Postoperative Case; Anesthesia for Pediatric Surgery; Disruption of Abdominal Wounds; and Surgery in Premature Infants. These few chapters set forth numerous principles of great importance, specifically for *pediatric* surgery.

The material is written in a clear, readable style and there is an excellent index. This text will find its greatest use by any surgeon who contemplates operations on children; who it has often been stated, "are not just little adults," and as a reference text for pediatrician and undergraduate medical student alike.

E. A.

CURRENT THERAPY edited by Howard F. Conn, M.D. Cloth. Eleventh Edition. 692 pages. Philadelphia and London: W. B. Saunders Co., 1955. $11.00.

This annual volume edited by Dr. Conn, with contributors from all parts of this hemisphere, is rather concise. The sections on The Infectious Diseases, Diseases of the Digestive System, and Diseases of the Skin are especially well written. Section Fifteen, Diseases due to Chemical and Physical Agents, is forward and contains a brief, but well-rounded discussion of the majority of toxicological conditions encountered by the average practitioner.

This text is probably one of the most complete of its kind. Therapeutics is not limited to any one field of medicine, but the diversity of the text makes it a rather unique reference.

H. A. B.

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REACTIONS WITH DRUG THERAPY by Harry L. Alexander, M.D. Cloth. 301 pages and 33 illustrations. Philadelphia and London: W. B. Saunders Company, 1955. $7.50.

Drug hypersensivity is a subject in which every practising clinician must be interested. Dr. Alexander concisely summarizes most of the known information regarding hypersensitive reactions, produced by the introduction of commonly used drugs into the human body. Several hundred such drugs, broken down into therapeutic categories such as: vitamins; antihistaminics; serums and vaccines, are collectively and individually discussed. In the first few chapters, generalized discussions are found of the specific types of reactions to be seen, with very adequate descriptions of the accepted theoretical mechanisms for their production. Under specific drugs are listed the types of reactions to be expected, with detailed references for those interested in more specific descriptions of the cases reported.

Perhaps the only unfavorable criticism that can be made of this book is that its value might be enhanced by addition of a more adequate discussion of the management of the reactions produced. Very little of such a discussion is included in the present edition. Totally, this book accomplishes its purpose quite well. It should receive wide popularity, as a handy reference book, to any physician who encounters what he believes may be a reaction to some drug he is administering; or to one who wishes to know in advance of the occurrence of such possible reactions.

E. A.

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CHRISTOPHER'S MINOR SURGERY edited by Alton Ochsner, M.D., F.A.C.S. and Michael E. DeBakey, M.D., F.A.C.S. Cloth. 7th edition. 547 pages with 251 illustratitons. Philadelphia and London: W. B. Saunders Company, 1955. $10.00.

This is the 7th edition of a book first published in 1929. This book is written by physicians who are on the teaching faculty of the Tulane and Baylor University medical schools. In it are discussed the numerous conditions considered as manageable by "minor surgical procedures"—that is, "management of surgical conditions which are usually associated with no immediate and little potential threat to life." The authors do a very fine piece of work in discussing those conditions whose management falls under the above criterion. The book is divided into eight sections, each one containing an anatomical system with the exception of the first which is devoted to general surgical considerations.

The book is prmarily oriented to instructing the student, undergraduate and postgraduate, in the diagnosis, preparation for surgery of, and actual technique of managing minor surgical cases. It is also ideally suited for the general practitioner and industrial physician who perform a great many of the so-called "minor surgical procedures." It enables them to become more technically familiar with information that they require, in a brief, accurate manner, that could only otherwise be obtained by long hours of laborious reading over large tomes of surgical procedure.

E. A.

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PERIPHERAL VASCULAR DISEASES by Edgar V. Allen, B.S., M.A., M.D., M.S., F.A.C.P., Nelson W. Barker, B.A., M.D., M.S., F.A.C.P:, and Edgar A. Hines, Jr., B.S., M.A., M.D., M.S., F.A.C.P. Cloth. 2nd Edition 825 pages and 316 illustrations. Philadelphia and London: W. B. Saunders Company, 1955. $13.00.

This is one of the few books devoted to a topic about which much is said and little is known. That a need for such a book exists, is the mere fact that a 2nd edition has been published. Much material has been added to the book particularly on the surgical management of the peripheral vascular diseases. Unfortunately some material, particularly that dealing with special methods of study, has been deleted from this edition. This is made excusable by the addition of much valuable information in its place.

Most diseases discussed are considered from the points of view of historical background, etiology, pathology and pathophysiology, symptoms, examination, applicable special methods of study, diagnosis and differential diagnosis and treatment. There are numerous references at the end of each chapter and a very adequate table of contents and index.

In their preface, the authors state two goals: "to aid the physician who must care for patients with peripheral vascular diseases, and to provide information for the student." This text admirably accomplishes both these goals and is well worth the purchase price for a surgeon's or internist's library as well as an excellent reference book for the student.

E. A.

ABSTRACTS SECTION

BASERGA, RENATO and BAUM, JOSEPH *(Dept. of Surg.; Div. of Oncology):* Induction of Blood-Borne Metastases by Tumor Transplantation in the Tail of Mice. Cancer Research. *15*:52-56, 1955.

A transplantable sarcoma of mice, which did not metastasize when implanted into the subcutaneous tissue of the trunk, yielded a high percentage of blood-borne metastases when transplanted into the subcutaneous tissue of the tail. This finding emphasizes the importance of the site of the primary growth in the spread of tumors by bloom stream.

The experiment also offers a simple technique for studying the mechanism of metastases: a.) It affords the possibility of obtaining metastases from otherwise non-metastasizing tumors. b.) It permits the removal of the primary growth with a simple procedure that reduces to a minimum trauma and bleeding, both being factors that influence the growth of metastases. c.) It is possible to investigate the third phase of blood-borne metastases, once the primary tumor has been removed, without acting upon the primary growth and without the disadvantages of the method of direct investigation of tumor cells in the circulation.

With such procedure it is possible to separate the factors that influence the penetration of tumor cells into the blood vessels from those that favor or inhibit the take of metastatic tumor emboli.

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BASERGA, RENATO and SAFFIOTTI, UMBERTO *(Dept. of Surg.; Div. of Oncology):* Experimental Studies on Histogenesis of Blood-Borne Metastases. Arch. Path. *59*:26-34, 1955.

C57 black mice, bearing a subcutaneous transplant of an anaplastic carcinoma (T150), showed a high incidence of blood-borne metastases in the lungs. The histological findings are summarized and conclusions regarding the metastatic behavior of Tumor T150 are drawn. Tumor emboli spontaneously released by the primary growth are most likely to consist of single or a few tumor cells. Such tumor emboli lodge in the pulmonary vessels either by adhering to the endothelium of arterioles or by "plugging" the lumen of capillaries. In arterioles their arrest is not due to a simple "plugging" of the lumen; but rather, the spread of tumor cells beyond the endothelial wall appears to be preceded by a phase of intraluminal growth. Signs of intraluminal growth were also detected in capillaries, although in this last case the possibility that occasional metastases might arise directly from extravasated tumor cells cannot be ruled out. In a few instances regressing and degenerating tumor-cell emboli were found in an intravascular position. No instance of regressing or degenerating extravascular growths was recorded.

Metastases originating from capillaries are more frequent than metastases originating from arterioles, the ratio being 2:1. The arteriolar walls can be invaded from the inside, and in arteries the tumor cells are capable of proliferating in the wall between the two elastic membranes.

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DASLER, WALDEMAR *(Assoc. Prof. of Biochem.):* Production of Experimental Lathyrism in the Rat by Two Different Beta-Substituted Ethyl Amines. Proc. of the Soc. for Exper. Biol. and Med. *88*:196, 1955.

1. Crystals which were isolated from sweet peas by a method which had previously yielded a toxic product were found to have the same infra-red absorption spectrum as synthetic Beta-aminopropionitrile sulfate.

2. Synthetic Beta-aminopropionitrile and Beta-mercaptoethylamine, when fed to rats as their hydrochlorides, produced skeletal changes similar to those caused by sweet peas. The mercaptoethylamine was the less effective in producing skeletal changes, although preliminary changes indicate, that it is at least as toxic as aminopropionitrile, when judged on the basis of lethality.

3. Some of the implications of these findings are discussed.

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FOA, P. P.; GALANSINO, G.; WEINSTEIN, H. R.; and MAGILL, A. M. *(Dept. of Physiol. and Pharm.):* Influence of Prolactin on Blood Sugar in Normal and Depancreatized Dogs. Amer. Jour. Physiol. *180*:313, 1955.

Eleven normal and five depancreatized dogs, in the post-absorptive state, received intravenous injections of prolactin (Armour 20 I.U./kg). In all normal animals the first prolactin injection caused a lowering of the blood sugar (mean=30%). Subsequent injections, given at intervals of 2 to 4 days, invariably caused hyperglycemia (mean =52%). Prolactin had no hypoglycemic effect in the depancreatized dog. In this animal, the first, as well as subsequent injections of prolactin, caused hyperglycemia (mean=55.5%). It is suggested that prolactin, at first, may stimulate insulin production, and that repeated injections may lead to exhaustion of the islets of Langerhans and to hyperglycemia. However, the hyperglycemia observed in the depancreatized animal indicates that prolactin may also exert its diabetogenic effect by some other mechanism, independent of the pancreas.

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GALANSINO, G.; FASOLI, A.; MAGILL, A. M.; and FOA, P. P. *(Dept. of Physiol and Pharm):* Serum Lipoproteins in Experimental Diabetes. IV. Effect of Prolactin. Proc. Soc. Exp. Biol. & Med. *88*:477, 1955.

Purified prolactin was injected intravenously into dogs in single or repeated injections. No significant changes in serum cholesterol, lipid phosphorus or lipoprotein pattern were noted in normal or depancreatized dogs; although prolactin caused marked changes in blood sugar concentration.

GALANSINO, G.; WEINSTEIN, H. R.; MAGILL, A. M.; and FOA, P. P. *(Dept. of Physiol. and Pharm.):* Rats Chronically Treated with Glucagon. Amer. Jour. Physiol. *180*:27, 1955.

Twenty adult rats received daily intraperitoneal injections of glucagon (Lilly) for periods of from 14 to 164 days. Twenty control rats received similar injections of saline. No significant changes were noted in glucose tolerance; insulin tolerance; glycogen content of liver, heart or gastrocnemius muscle; serum cholesterol; lipid phosphorus and lipoprotein pattern; number and appearance of Alpha and Beta cells of the islets of Langerhans; and weight or morphological appearance of heart, liver, pancreas, pituitary and adrenals. Glucagon appears to be non-toxic and, in particular, non-diabetogenic.

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GOLDBERG, S. E. and CLARK, GEORGE *(Former Assoc. Prof. of Anat.):* "Relational" vs. "Specific Stimulus" Learning in Discrimination. J. of Genetic Psychology. *86*:187, 1955.

Pigmented rats were trained to discriminate between two sizes of white rings on a black background. They were then presented with two rings identical in size to either the larger or the smaller of the two previously used. Jumping latencies were significantly greater for the previously negative targets as compared to those for the previously positive targets. This confirms, for a pattern discrimination, the work of Webb ('50) with a brightness discrimination. However, reasons are presented for not considering this to be a crucial test between "specific stimulus" theories and "relational learning" theories of discrimination learning.

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LUNSKEY, LOUIS L. *(Alumnus, 1950):* Murderous "Acting Out" as a Primitive Defense to Master Anxiety. Amer. J. of Psychotherapy. *IX*:2, p. 262-268. April, 1955.

The schizophrenic process is a regressive adaptation in which the individual attempts to cope with overwhelming anxiety. This eruption may precipitate a state of fugue, the personality becomes fragmented, cultural accertions become lost, and primitive patterns of behavior gain sway.

Delusions, hallucinatory phenomena and ideas of reference are attempts to cope with feelings of anxiety. At times these operations are not successful, and the psychotic is not able to create a state of omnipotence by these restitutive measures. The only primitive pattern which will ameliorate this state of terror is intense motor activity culminating in direct aggression towards a representative of a past significant figure. By this method, the barrier to omnipotence is eliminated, and the significant object is destroyed by this symbolic act.

A schizophrenic case history is presented in which anxiety is mastered by assaultive murderous behavior.

FOA, P. P. *(Prof. of Physiol. and Pharm.),* and GALANSINO, G.: Il Glucagone. Progressi Medicina Interna. *17*:421, 1955.

A critical review written in Italian.

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SAIDEL, LEO J. *(Assist. Prof. of Biochem.):* Ultra-violet Absorption Spectra of Peptides. I. Compounds Containing a Single Monoalkyl-Substituted Amide Link. Arch. of Biochem. and Physics. *54*:184, 1955.

1. Spectra in the ultra-violet region from about 200 or 240 mu are represented for aqueous solutions of the following compounds at various pH values: (a) acetyl and/or glycyl derivatives of nearly all of the amino acids which commonly occur in proteins; (b) a number of isomeric dipeptides with the sequence of the residues reversed; and (c) glycine amide, pyrrolidone carboxylic acid, and N-monomethylacetamide.

2. The attempt is made to consider the spectrum of a dipeptide as the resultant of interactions between the peptide link and other groups which may occur on the molecule, *viz.,* a terminal carboxyl group, a terminal amino group, and various specific amino acid side chains.

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WERCH, S. G. *(Assoc. Prof. of Med.);* MARQUARDT, G. H.; and MALLACH, J. F.: The Action of Trichlorethylene on the Cardiovascular System. Amer. Jour. of Obst. and Gyne. *69*:352, 1955.

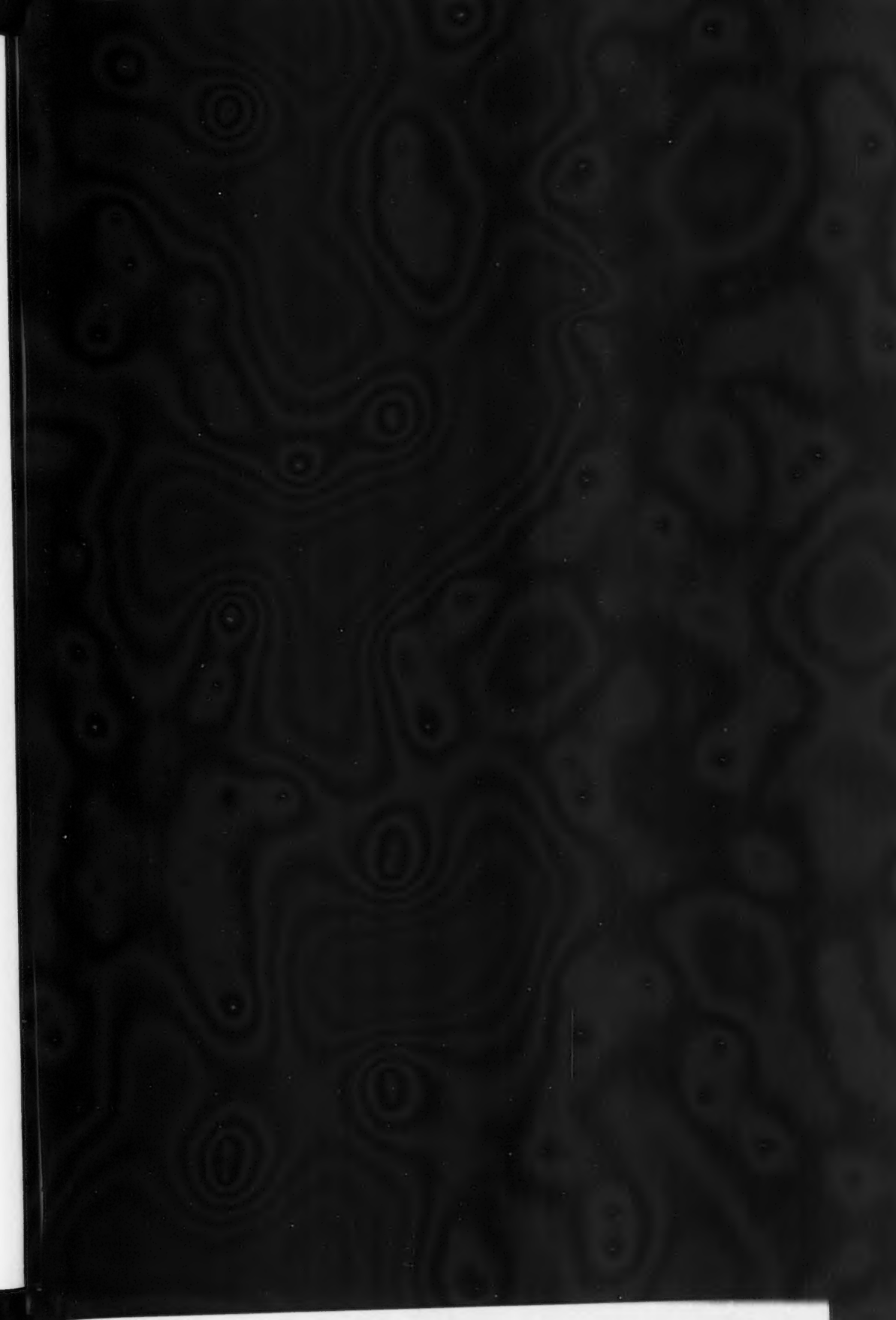
Trichlorethylene affects both the myocardium and conducting mechanism of the heart, when used repeatedly or in comparatively large amounts. The administration, by inhalation, of a single therapeutic dose, 1.0 c.c. of the drug, however, is not harmful to the human heart.

The primary effect of trichlorethylene on blood pressure is depression, and the probable mechanism is splanchnic dilation.

The effects on respiration, kidney volume, capillary size, and coronary flow are probably due to multiple causes, *i.e.,* blood pressure, heart rate, and rhythm. The respiratory rate is increased, volume is lowered, capillary constriction occurs, the coronary flow decreases, and irregularities in rate and rhythm are observed.

The benefits reported from the use of trichlorethylene in angina pectoris are not supported by this investigation. If migraine is due to capillary vasodilation, then the action of the drug on capillaries may explain the benefits reported in this condition. Since there is considerable danger in the concomitant blood pressure depression, any value obtained from its action on capillaries is overbalanced.

Since comparatively large amounts of trichlorethylene may be administered, *i.e.,* as an analgesic agent during labor, it may be well to warn of the untoward cardiovascular effects that may occur.



THE CHICAGO MEDICAL SCHOOL

QUARTERLY

710 SOUTH WOLCOTT AVENUE

Chicago 12, Illinois

The Chicago Medical School *QUARTERLY* is published four times yearly by the Chicago Medical School for the dissemination of current medical news and for the advancement of medical science with a student staff under the supervision of a faculty editorial board.

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